POLYPHARMACY IN OLDER ADULTS: A MULTI-LEVEL ANALYSIS OF TRENDS AND DETERMINANTS IN SAO PAULO, BRAZIL

by

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ABSTRACT

Background: Polypharmacy, the excessive use of prescription drugs, is a growing worldwide phenomenon, especially among older adults. There is no consensus among clinical communities regarding how many drugs are too many. In general, a threshold of five or more drugs is used to define polypharmacy because it has been shown to correlate with an increased risk of adverse effects and mortality. Polypharmacy exposes individuals to increased risk of adverse effects, drug interactions, and adverse clinical outcomes such as falls, frailty, and mortality. This is a special challenge among older adults, who have less metabolic reserve and may be more susceptible to drug risks. Because public resources are often spent to provide or subsidize older adults' pharmaceutical treatments, polypharmacy is also a matter of appropriate management and rational use of public resources. These questions are especially relevant in the context of low-and middle-income countries, where the demands of rapidly growing aging populations pose significant burden on public health systems, but where scarce resources are divided between multiple sources of disease burden such as maternal-child conditions, infectious disease and other critical needs.

Aims: In this study, we examine the occurrence of polypharmacy among older adults living in Sao Paulo, Brazil. We explore temporal trends in polypharmacy over a period of 10 years and geographic variations in the prevalence of polypharmacy across Sao Paulo's thirty administrative areas. We investigate the extent to which polypharmacy is associated with increased risk of drug-related problems in this context and we investigate possible determinants at the individual, community, and health system's levels.

Methods: We combine individual-level data from a survey of older adults age 60 years and over living in the community in Sao Paulo (the SABE Study) with data from official government sources to implement multi-level latent variable mixed-effects analytical models in order to estimate the association between polypharmacy and community and health systems factors while controlling for individual characteristics.

Results: The prevalence of polypharmacy among Sao Paulo older adults doubled from 16% to 38% in the 10-year period. Drug risk was frequent, and strongly associated with higher numbers of drugs per day. About two-thirds of people with polypharmacy were exposed to some form of risk. Levels of inappropriateness among people with polypharmacy tended to decrease over time, but drug interactions and anticholinergic risk tended to

increase. Polypharmacy was associated with having greater number of chronic diseases, being in worse health, using greater levels of health services, being older, and being female. There was significant geographic variation in polypharmacy across areas. Individual characteristics explained most, about 25%, of the variation in drug utilization. At the health system level, polypharmacy was associated with Presence of hospitals, higher number of private pharmacies, and higher enrollment in the family health program after controlling for individual characteristics. Having private health insurance did not change the likelihood of polypharmacy, but living in an area with higher health insurance coverage greatly increased the likelihood of polypharmacy. Higher number of doctors in the public health system was associated with lower polypharmacy. Polypharmacy is likely a combination of patient preferences and health need, as well as provider practices, and the constraints and limitations of the health system where they interact.

Conclusion: polypharmacy among older adults should be a matter of public health concern in Sao Paulo. Understanding that not all polypharmacy is driven by need is important in order to devise strategies to improve monitoring and provide opportunities for review and discontinuation of treatments. Policies to reduce drug risk should target all older adults with polypharmacy.

PREFACE

It was a typical day in Hospital de Clinicas, the public hospital in Southern Brazil where I trained as a neurologist. Carmela was coming to see us for a long-standing hand tremor that made her life very challenging. Carmela was taking more than ten different drugs every day to treat a multitude of health problems. I found that Carmela's tremor was caused by one of the drugs she was taking, which she should stop immediately. Carmela was surprised and hesitant. She had been taking these drugs for many years. It was the first time in her life that a doctor said she should stop taking medications instead of prescribing more of them.

Patients like Carmela were very common. In the booming Brazilian economy, with its thriving generic industry and its government programs providing improved access to medicines, patients like Carmela were increasingly able to access medications and unfortunately many of them got on polypharmacy regimens. Because of the fragmented medical care system, polypharmacy received little monitoring.

Once I completed my clinical training I was working with a team of policy-makers at the state health administration championing appropriate access to medicines. The experience of patients like Carmela convinced me that increasing drug access without adequate monitoring was wasteful of health resources, provided an unnecessary financial burden on patients and families, and could lead to adverse outcomes.

I came to the Doctoral program in International Health - Health Systems at Johns Hopkins committed to researching ways to safeguard sustainable and qualified access to medical treatment for individuals with chronic diseases in low- and middle-income countries. With this dissertation, my main goal is to contribute to clarifying the drivers and potential solutions of growing pharmaceutical use among older Brazilian adults. Ultimately, I hope this work contributes to inform public health policies aimed at mitigating the risk from polypharmacy and inappropriate medication use in Brazil.

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In my trajectory this far I have had the opportunity of working with brilliant mentors and colleagues who shaped my work as a physician, a scholar and a public health professional. I am especially grateful to my advisor, Prof. Gerard Anderson, for his enthusiasm, encouragement, and for his relentless efforts to help me find and focus on the most important questions, both in research and in life. Working alongside Jerry has provided me with many invaluable lessons, from how to be an engaging and inspiring leader, to how to produce research that is relevant and actionable. I am also very grateful to the members of my dissertation committee, Profs. Elizabeth Stuart, David Peters and Caleb Alexander. Their advice, thoughtful feedback, and questions challenged me to pursue excellence in every step of this work. I am also grateful for the support of Profs. Ge Bai and Krishna Rao, who served as alternate members of the final exam committee.

This work benefitted immensely from the expertise and advice of Prof. Elizabeth Colantuoni, who introduced me to the enigmas of multi-level modeling, and Prof. Antonio Trujillo, who helped me conceptualize the research project and who incentivized me to implement complex and advanced methodologies to the context of developing countries. I am very grateful for the support and mentorship of both. I am also grateful to Prof. Maria Lúcia Lebrão (in memorian), from Universidade de São Paulo, for allowing me to use the valuable data collected by her team in the gigantic effort that was the SABE Study.

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Teaching represented a great part of my experience throughout the doctoral program. I am thankful to the many professors who had me as their teaching assistant and who taught me in so many ways to be a better educator: Profs. Marie Diener-West (Biostatistics), Louis Niessen (Comparative Health Policy and Economic Evaluation),

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I am grateful to the Johns Hopkins Krieger School of Arts and Sciences for allowing me to independently develop and teach a course on Health Systems Challenges from Chronic Diseases in Low and Middle-Income Countries, which I taught to Public Health Studies undergraduates in 2013 and 2015. I am also grateful to the Johns Hopkins Preparing Future Faculty Teaching Academy, which provided me with solid training on the science of teaching in higher education and allowed me to explore teaching as research. I am especially grateful to Michael Reese for his advice and support throughout this process.

I thank the students in the multiple courses where I served as a teaching assistant, and especially the dedicated undergraduate students who took my courses. I am very grateful for all that I learned from them, and watching their trajectories unfold with so many successes fills me with great joy and enthusiasm.

I benefitted immensely, over the years, from the teaching and mentorship of brilliant and generous scholars who shared their knowledge and advice and helped guide me through difficult life and academic decisions. I am especially grateful to Prof. João Biehl from Princeton University. I first met João while I was working with state attorneys in the Rio Grande do Sul public health administration, in Southern Brazil. João was implementing an ambitious research project to investigate the judicialization for access to medicines in the local context. The opportunity of joining João's research team changed my life forever, as it allowed me to expand my perspective on health and health care way beyond the biomedical model that I was exposed to as a physician, introducing me to the complex relationships between individuals and society, helping me become a more humane clinician and researcher, and ultimately helping me develop my own trajectory as an independent scholar. I am also immensely grateful for the invaluable advice, support and mentorship that I received from Profs. Adriana Petryna and Joseph Amon during the many years of collaboration.

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The education that I received from Universidade Federal do Rio Grande do Sul (UFRGS), in Porto Alegre, Brazil, has been the cornerstone of all my academic pursuits. I am extremely grateful to this world-class institution for providing me with excellent medical training, numerous research opportunities, a specialization in Neurology and, most importantly, a critical view of medicine and science. I must also mention that UFRGS is not only one of the best academic institutions in Brazil; it is also tuition-free. This institution is an invaluable resource for our society and my gratitude and my admiration for it are immeasurable.

At UFRGS I had the opportunity to learn from and train with many medical experts, especially in Neurology. I am very grateful to Profs. Márcia Chaves and Fernando Kowacs for giving me my first opportunities to participate in research. I am also very grateful to Prof. Paulo Picon for introducing me to the realities of policy-making in the Brazilian health care system, for teaching me the value and the limitations of evidence-based medicine, and for giving me the opportunity of working hands-on to improve access to high-cost medicines in Brazil. I am very grateful to Neurogeneticist Prof. Laura Jardim for her brilliant guidance throughout my Master's of Science research project investigating the genetics of early-onset Parkinson's disease in Southern Brazil. I am also very grateful for the invaluable mentorship and unwavering support of Neurologist Prof. Carlos Rieder throughout my training in Neurology, my Master's thesis research, and throughout my medical and research career since then. Prof. Rieder, a specialist in Movement Disorders, first introduced me to the severe drug-induced conditions such as tremor and parkinsonism that have motivated my work ever since, including this dissertation. Profs. Rieder and Jardim are examples of what I aspire to be as a researcher and as a physician. Their excellent work inspires me every day, and I wish to continue our collaborations for many years to come.

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1. CHAPTER I: INTRODUCTION AND BACKGROUND

1.1 INTRODUCTION

Polypharmacy, the excessive use of prescription drugs, is a growing worldwide phenomenon, especially among older adults. There is no consensus among clinical communities regarding how many drugs are too many. Clearly, there are patient circumstances that will determine the need for certain drugs. Studies have also shown that provider characteristics and the availability and type of health insurance can influence the number of drugs prescribed. In general, a threshold of five or more drugs is used because it has been shown to correlate with an increased risk of adverse effects and mortality. Polypharmacy exposes individuals to increased risk of drug-related problems such as adverse effects and drug interactions, as well as adverse clinical outcomes such as falls, frailty, cognitive impairment and mortality. This is a special challenge among older adults, who have less metabolic reserve and may be more susceptible to drug risks. Mismanagement of drug-related problems may result in more drugs being prescribed, compounding the risks without adding benefits. Depending on level and type of health insurance benefits, polypharmacy may use up financial resources, which can be especially burdensome for older adults, who generally have fixed incomes.

Because public resources are often spent to provide older adults' drug treatments, polypharmacy is also a matter of appropriate management and rational use of public resources. These questions are especially relevant in the context of low-and middle-income countries (LMICs), where the demands of rapidly growing aging populations pose significant burden on public health systems, but where scarce resources are divided between multiple sources of disease burden such as maternal-child conditions, infectious disease and other critical needs.

In this study, we examine the occurrence of polypharmacy among older adults living in Sao Paulo, Brazil. We explore temporal trends in polypharmacy over a period of 10 years (2000-2010) and geographic variations in the prevalence of polypharmacy across the thirty administrative areas of the city of Sao Paulo (sub-prefectures). We investigate the extent to which polypharmacy is associated with increased risk of drug-related problems in this context. We use multi-level analytical models to investigate the association between polypharmacy and

determinants at the individual and at the community level, including societal and health system characteristics. The objective is to provide evidence to support public health decision-making to mitigate the growing problem of polypharmacy. Identifying the main drivers of this phenomenon is of key importance to policy-makers who may want to develop strategies to mitigate it.

1.2 BACKGROUND

1.2.1 Policy Problem: Polypharmacy

There is evidence from multiple countries around the world that people are taking medicines more often and in progressively higher quantities. Although there is no consensus regarding how many drugs constitute polypharmacy, it has been demonstrated that the concomitant use of five or more drugs per day exposes individuals to substantial risks regardless of the specific drugs involved (Gnjidic et al., 2012; Langeard et al., 2016). Each individual drug that is added to a regimen has been associated with 7% increase in the odds of falls, 8% increase in the odds of disability, 13% increase in the odds of frailty and 9% increase in the odds of mortality (Gnjidic et al., 2012). Regimens of five or more have been found to be a sensitive and specific marker of increased risk of physical and cognitive impairments (Langeard et al., 2016). When the number of drugs per day reaches 10 or more it is usually considered excessive polypharmacy (Jyrkka, Enlund, Korhonen, Sulkava, & Hartikainen, 2009a).

Polypharmacy may reflect the need to treat increasingly complex and multifactorial chronic conditions (Appleton, Abel, & Payne, 2014). Some diseases have multiple causative pathways and demand multiple drugs for their appropriate management. This is the case of cardiovascular disease, the most common cause of death of older adults in the world (Sepulveda & Murray, 2014). Other diseases occur in frequent combinations, each requiring a separate therapy (Aronson, 2004; Gurwitz, 2004).

Polypharmacy has been associated with increased risk of adverse effects and drug interactions (Buck et al., 2009; Doan, Zakrzewski-Jakubiak, Roy, Turgeon, & Tannenbaum, 2013; Routledge, O'Mahony, & Woodhouse, 2004; Saedder, Lisby, Nielsen, Bonnerup, & Brock, 2015); clinical conditions such as frailty, falls, cognitive decline and disability ((Bowling et al., 2013; Faller et al., 2017; Jyrkka, Enlund, Lavikainen, Sulkava, &

Hartikainen, 2011; Payne, Abel, Avery, Mercer, & Roland, 2014); avoidable hospitalizations, and increased mortality (Gomez et al., 2015; Richardson, Ananou, Lafortune, Brayne, & Matthews, 2011). Misdiagnosis of drug-induced problems may trigger the prescription of additional drugs instead of the discontinuation of the offending drug. The prescription of additional drugs to treat drug-induced conditions is called a prescription cascade and is a serious public health problem particularly associated with polypharmacy (Hunt, Kreiner, & Brody, 2012; Rochon & Gurwitz, 1997).

High drug expenditures make polypharmacy a matter of concern for financial protection in health systems. Drugs tend to consume a significant proportion of household budgets (Cahir et al., 2010; Hovstadius & Petersson, 2013; Lima, Ribeiro, Acurcio Fde, Rozenfeld, & Klein, 2007; Lima-Costa, Barreto, & Giatti, 2003). Older adults tend to have lower incomes and tend to use more drugs, so the financial burden from drugs is of special concern among this population. In Brazil, drug expenditures among older adults amount to, on average, 51% of the national minimal wage (Lima et al., 2007). Drug expenditures may deplete financial resources that older adults could otherwise use towards self-care, nutrition and other needs (Fang, Nicholas, & Silverman, 2010).

Polypharmacy also poses significant challenges to medication adherence and self-management. The chronic stress from taking drugs, disruptions to treatment adherence, and depletion of financial resources are non-drug-related pathways through which polypharmacy may impact quality of life (Hovstadius & Petersson, 2011).

Because public health resources are often employed to provide or subsidize pharmaceutical treatments for older adults, the growing use of polypharmacy among the older population is also a matter of concern to public health decision makers, as it poses questions about appropriate allocation of public health resources.

1.2.2 Definition

In this study we define polypharmacy as the use of five or more prescription or over-the-counter drugs per day. In some analyses we use a more conservative threshold of ten or more prescription or over-the-counter drugs per day.

Most studies of polypharmacy include prescription and over-the-counter drugs in their analyses but do not include nutritional supplements, herbal, or homeopathic medicines. Our definition includes prescription and over-the-counter drugs that are both orally and topically administered (skin, ocular, otologic, or inhaled drugs). Our definition includes topical-use drugs because they add complexity to treatment regimens, and we assume these drugs can have systemic effects once they have been absorbed.

We do not include does not include nutritional supplements, herbal, or homeopathic medicines in our analyses. These drugs are not standardized in terms of manufacturing practices and chemical composition, so that comparisons across these substances may not be reliable. We assume that the effect of polypharmacy was independent from herbal and homeopathic medicines.

1.2.3 Inappropriate Polypharmacy

All cases of polypharmacy are associated with increased drug-related risks because each drug adds a set of potential adverse effects and increases the risk of drug interactions (Buck et al., 2009; Doan et al., 2013; Saedder et al., 2015). There are drugs and drug combinations, however, that are known to have a particularly undesirable risk profile. These drugs have been labeled "potentially inappropriate medications" or "potentially inappropriate prescriptions" (Fick et al., 2003).

In our study we label as "inappropriate polypharmacy" the cases where an individual taking five or more drugs per day also meets at least one criterion for increased drug risk: a potentially inappropriate medication, a potential drug interaction, or increased risk of anticholinergic adverse effects. With this differentiation we aim to identify regimens that may be associated with higher risks than general cases of polypharmacy. Potentially inappropriate medications are drugs that should be avoided in all older individuals because they "*pose unnecessarily high risk*" (of adverse effects and drug-drug interactions) or are likely to be "*ineffective*" among this population (Fick et al., 2003). [1] There are additional drugs that are considered inappropriate only among

[1] The definition of what constitutes an "older adult" varies across contexts. In developed countries it is usually accepted to be 65 years of age. In developing countries it is usually accepted to be 60 years of age. In this study we use the definition of 60 year olds and over.

persons with certain underlying medical conditions (Fick et al., 2003). However, these are outside of the scope of our study. In order to identify potentially inappropriate medications we use the 2012 update of the Beers Criteria, a tool that lists over a hundred drugs that should be avoided among older adults (American Geriatrics Society Beers Criteria Update Expert, 2012).[2] All the tools used to define inappropriate polypharmacy in our study were developed specifically for the population of older adults and have been demonstrated to identify individuals at risk independently of whether any symptoms or signs have occurred.

Drug interactions are defined as a situation in which there is a "*clinically meaningful alteration in the effect of one drug as a result of co-administration of another (precipitant drug)*" (Hines & Murphy, 2011). Some drug interactions may be desirable, for example when the beneficial effects of a drug are enhanced by another. However, some interactions may reduce therapeutic effects or increase toxicity. Undesired drug interactions can have mild to severe clinical consequences, and their diagnosis is often challenging. A combination of drugs that is known to be associated with undesired effects is called a potential drug interaction and it is considered a matter of concern even if no symptoms have yet occurred (Hines & Murphy, 2011). In this study we use the Hines list, a tool that identifies seventeen drug combinations associated with increased risk of hospitalization or mortality among the elderly, to identify cases of potentially harmful DDIs (Hines & Murphy, 2011).

Adverse drug effects are: *"a response to a drug that is noxious and unintended and occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function"* (Edwards & Aronson, 2000). There are several mechanisms through which adverse effects occur. They may be dose-related (toxicity), non-dose-related (idiosyncratic), time- and dose-related (cumulative effects), time-related (occurring some period after the use of the drug), withdrawal-related, or unexpected failure of the therapy (Davies, 1977; Edwards & Aronson, 2000). The severity of adverse effects can range from mild to very severe, including death.

There is not one single definition of symptoms that constitute adverse effects. This is because what is considered an adverse effect in one context may be desirable in another. In this study we chose to focus on anticholinergic adverse effects. These symptoms are clinically diverse and can be very severe, especially among older

[2] Chapter III – Polypharmacy and Drug Risk – describes each tool and classification in more detail.

individuals. Also, anticholinergic adverse effects can be triggered by a wide variety of drugs used to treat diverse conditions and organ systems.

Anticholinergic symptoms arise when drugs interfere with acetylcholine, a chemical messenger involved in many different pathways in most organ systems of the body. Examples of peripheral anticholinergic adverse effects are those related to reduce production of saliva and tears (dry eyes, dry mouth), or reduced movements of the gut and bladder (constipation, urinary retention). Examples of central anticholinergic adverse effects are somnolence, memory problems, confusion and inability to concentrate. Anticholinergic adverse effects may be very severe and may cause falls, severe cognitive decline, hallucinations, hospitalizations, and even death.

In order to identify patients at risk for anticholinergic adverse effects in this study we utilize the Anticholinergic Risk Scale (ARS). The ARS comprehends an extensive list of frequently used drugs that are assigned a score from zero (limited or no anticholinergic potential) to three (very strong anticholinergic potential) based on findings from the medical literature, from FDA records, and from the chemical activity on the anticholinergic receptor (Rudolph, Salow, Angelini, & McGlinchey, 2008). There are other tools to evaluate anticholinergic adverse effects, but we chose the ARS because it performs better to identify individuals at high risk of severe anticholinergic adverse effects such as impaired cognitive and functional performance (Pasina et al., 2013)

1.2.4 Polypharmacy in Older Adults – Prevalence and Trends

The growing pharmaceutical use among older adult populations has been more extensively documented in high-income countries. Nevertheless, it may also be a concern for developing countries, whose populations are aging at a fast pace. In fact, growing use of pharmaceuticals may be of special concern for developing countries, because expanded access to medicines may not be accompanied by adequate drug regulations, monitoring and surveillance in these settings.

Although the specific rates vary across studies, it is clear that a very high proportion of older adults take at least one medicine per day (Table 1.1). The prevalence of taking at least one medicine per day tends to be higher among studies of older age groups. For example, up to 98% of individuals aged 75 years and over were found to

take at least one drug at a daily basis in Finland (Jyrkka et al., 2009a). The prevalence of polypharmacy varies across settings, age groups, and with different definitions of polypharmacy (different cutoff points and duration of the pharmaceutical use).

In this section we focus on describing prevalence and trends in polypharmacy worldwide. We discuss the factors that may underlie these trends in later sections.

Among persons age 65 and older, an estimated 29.5% took five drugs or more in France (an average rate between 1995 and 2004) (Bongue et al., 2009), 46% in Italy (Nobili et al., 2011), and 53% in the United States (Linton, Garber, Fagan, & Peterson, 2007). The prevalence of polypharmacy was 34% in Costa Rica among those 60 year-olds and over (Jiménez Herrera & Fernández Rojas, 2008). The rates of polypharmacy in studies from Asian countries stand out. In Korea as much as 86.4% of individuals 65 years and older took six drugs or more per day (Kim, Shin, Kim, & Park, 2014). In Taiwan, 81% of individuals 65 years and older in Taiwan took five or more drugs at some point during the last 12 months, and 32.5% were with polypharmacy for at least 6 months of the year (Chan, Hao, & Wu, 2009).

Excessive polypharmacy was present in 23% of older adults in Finland (Jyrkka et al., 2009a) and 38% in Taiwan (Chan et al., 2009)(both defined as ten or more drugs a day), and about 45% in Korea (defined as 11 or more drugs per day) (Kim et al., 2014)

All studies that analyzed trends in drug use over time have found significant growth in the rates of polypharmacy (Table 1.1). Rates of change varied according to the population age, baseline values, and years studied. Between 1990/91 and 1998/99 the rates of polypharmacy grew more than 30% among Finnish individuals aged 65 and over, from 19 to 25% (Linjakumpu et al., 2002). Between 2000 and 2010 there was over 20% growth in polypharmacy rates among Italians of the same age group, from 42.8 to 52.7% (Franchi et al., 2013). In Sweden, rates of growth in a period of three years were higher for excessive polypharmacy (15%) than for polypharmacy (4%), probably because of the markedly lower baseline prevalence of excessive polypharmacy (9%) as compared to polypharmacy (39%) (Hovstadius, Hovstadius, Astrand, & Petersson, 2010).

Table 1.1 Studies that estimated point prevalence of polypharmacy among community-dwelling older adults

Author, year	Country	Year(s) data was collected	Participants	Prevalence	Factors associated with polypharmacy
Jyrkka, 2009	Finland	1998	Age ≥75 N=535	≥1 drug: 98% ≥ 6 drugs: 57% ≥10 drugs: 23%	Age ≥85 Female gender Chronic diseases Poor perceived health
Bongue, 2009	France	1995-2004	Age ≥65 N>30,000	≥1 drug: 84% ≥5 drugs: 29.5%	
Chan, 2009	Taiwan	2001-2002	Age ≥65[1] N=11,788	≥5 drugs[2]: 81% ≥10 drugs: 38.1% "persistent polypharmacy ≥5 drugs[2]: 32.5%	Age <85 years Male gender Chronic diseases Poor physical function Living in urban area Visiting multiple providers Hospital-affiliated care Use of co-pays
Jimenez-Herrera, 2008	Costa Rica	2004	Age ≥60 N=2,820	≥1 drug: 78.7% ≥5 drugs: 34%	Higher age Female gender Chronic diseases Place of residence (metropolitan area)
Linton, 2015	USA	2004-2005	Age ≥65 N>1.3 million	≥1 drug: 77% ≥5 drugs: 53%	Female gender
Qato, 2008	USA	2005-2006	Age 57-85 N=2,976	≥1 drug: 81% ≥5 drugs: 29%	Male gender Age 75-85
Nobili, 2011	Italy	2005	Age ≥65 N>1.8 million	≥1 drug: 88% ≥5 drugs: 46%	Higher age Female gender Place of residence (clusters of higher prevalence)
Kim, 2014	South Korea	2010-2011	Age ≥65 N>320,000	≥6 drugs: 86.4% ≥11 drugs: 44.9% ≥21drugs: 3%	Age 70-84 Male gender Chronic diseases Higher number of medical visits Supplemental insurance

Notes: [1]: not all the study population lived in the community. However, those living in the community had higher prevalence of polypharmacy than those institutionalized. All individuals had impairment in least one activity of daily living or an instrumental activity of daily living. [2]: polypharmacy was the use of 5 or more drugs at any point of the year, and persistent polypharmacy was the use of 5 or more drugs for over 180 days in a year.

Table 1.2 Studies that estimated changes over time in prevalence of polypharmacy among older adults

Author, year	Country	Years data was collected	Participants& Location	Prevalence	Factors associated with polypharmacy
Linjakumpu, 2002	Finland	1990/91 - 1998/99	Age ≥65 N=1,131 N=1,197 Lieto municipality	≥5 drugs: 19→25% avg. drugs 3.1→ 3.8 /day	Higher age Female gender Poorer perceived health status
Franchi, 2013	Italy	2000-2010	Age ≥65 N>2 million Lombardy Region	≥1 drug: 88→ 90.3% ≥5 drugs: 42.8 → 52.7%	Higher age Female gender *Males had lower baseline prevalence but greater rates of change
Hovstadius, 2010	Sweden	2005-2008	All ages N>9 million	Among ≥60 year-olds: ≥1 drug: 76→ 78% ≥5 drugs: 39.4 → 40.9% ≥10 drugs: 9.05 → 10.9%	Higher age Men had greater rates of increase

1.2.5 Polypharmacy in Older Adults - Geographic Variation

Geographic variation analyses recognize that there may be significant differences in the prevalence of polypharmacy across areas at the subnational level. Geographic variation studies have helped identify the role of supply-side factors in influencing the utilization of polypharmacy (Table 1.3).

Studies of geographic variations of polypharmacy at the small area/sub-national level have found differences in the prevalence of polypharmacy among older adults of up to 26% across areas (Franchi et al., 2013). In a same geographic area, polypharmacy rates tended to be highly correlated over time (Cashion et al., 2015; Franchi et al., 2013; Perry & Turner, 2001). Areas that stood out as clusters of high prevalence in a given year tended to remain the ones with highest prevalence even after a period of ten years – this was the case of Southern states in the USA and parts of the Lombardy region in Italy (Cashion et al., 2015; Franchi et al., 2013; Perry & Turner, 2001).

Table 1.3 Geographic variation studies of polypharmacy in older adults

Author, year	Country	Year data collected	Population	Prevalence difference across areas (Range)	Factors associated with higher rates of polypharmacy
Perry, 2001	USA	1988-1994	Sample of Individuals Age ≥65 Nationwide N=5,249	Polypharmacy ≥5 drugs 1.8% (17.8-19.6%)	Higher age Female gender Higher income and education Southern region Number of physician visits was not associated when controlling for the above
Hovstadius, 2010	Sweden	2006	Entire population All age groups Nationwide	≥1 drug 5.1% (40.9–46.0%) ≥5 drugs 3% (9.1–12.1%) ≥10 drugs 1.7% (1.9–2.6%)	Higher age Poorer health of adult population (24-64 year olds) Negative correlation with higher education levels and higher number of doctors per 100,000 population
Franchi, 2013	Italy	2000-2010	Aggregate of individuals Age ≥65 Lombardy Region (Northern Italy)	Chronic[1] Polypharmacy ≥5 drugs 10% in 2000 (0 - 10%) 26.6% in 2010 (0 - 26.6%)	Strong correlation over time in prevalence for each area [2] Low correlation with health status (deaths, hospitalization)
Kim, 2014	South Korea	2010-2011	Aggregate of Individuals Age ≥65 Nationwide	Polypharmacy ≥6 drugs 3.5% (86.9-90.4%) Age-adjusted	Use of medical visits strongly associated with higher polypharmacy
Cashion, 2015	USA	2003-2007	Aggregate of Individuals Age ≥45 Nationwide	Polypharmacy ≥8 drugs 6.3% (13-19.3%)	Female gender White race Southern states Variation persisted after controlling for gender, age, income, education, and comorbidities

1: Chronic polypharmacy: "*five or more drugs in 1 month for at least 6 months (consecutive or not) in a year*". 2: the authors hypothesize that the correlation for the same area over time may be explained by some overlap in the patient population and/or by doctors maintaining similar prescription patterns over time in each area.

1.2.6 Individual-Level Determinants of Polypharmacy

Tables 1.1 and 1.2 display the studies that investigated the association between polypharmacy and individual characteristics. Gender was found to be associated with polypharmacy in virtually all studies, even after adjusting for confounders such as age and presence of chronic diseases. However, while most studies identified that females had more polypharmacy, some studies found that males were more likely to have polypharmacy (Chan et al., 2009; Kim et al., 2014; Qato et al., 2008). Interestingly, two of the studies that found higher prevalence of polypharmacy among males were from the Asian region (Chan et al., 2009; Kim et al., 2014). It is not clear why gender is associated with polypharmacy. Patterns of disease occurrence, care-seeking behavior, and beliefs and preferences related to acceptability of drug treatments are some of the underlying characteristics that could help explain the differences in polypharmacy observed across genders. Women are more likely to live to older ages and are more likely to have chronic diseases, including multi-comorbidities(Miilunpalo, Vuori, Oja, Pasanen, & Urponen, 1997). Women are more likely to seek care, and could also be more likely to accept and to adhere to pharmaceutical treatments, or even to self-medicate (Miilunpalo et al., 1997).

Age was associated with polypharmacy across the multiple studies, even after adjusting for other variables. Because higher age is strongly associated with greater prevalence of chronic conditions, as well as higher rates of functional limitations, it is important to control for these conditions when investigating the association between age and polypharmacy. Some studies found that any increases in age were associated with greater polypharmacy (Franchi et al., 2013; Hovstadius, Astrand, & Petersson, 2010; Hovstadius, Hovstadius, et al., 2010; Jiménez Herrera & Fernández Rojas, 2008; Linjakumpu et al., 2002; Nobili et al., 2011). Others found that specific age ranges, either at the middle or at the higher end of the age distribution, were most at risk (Jyrkka, Enlund, Korhonen, Sulkava, & Hartikainen, 2009b; Kim et al., 2014; Qato et al., 2008). One study found higher polypharmacy in the relatively younger age group (Chan et al., 2009).

Poorer health was measured in different ways across studies: higher number of comorbidities (Chan et al., 2009; Jiménez Herrera & Fernández Rojas, 2008; Jyrkka et al., 2009b; Kim et al., 2014), worse perceived health status (Jyrkka et al., 2009b; Linjakumpu et al., 2002), and increased disability (Chan et al., 2009). All the different metrics of poor health were associated with greater polypharmacy. These results indicate that, from a population perspective, older populations with more frequent and multi-comorbid chronic conditions may be the strongest

demand-side drivers of polypharmacy. Although it is not clear whether these factors act independently from each other or whether they may modify each other's associations.

Other findings suggest that factors beyond the individual level may independently affect the likelihood of polypharmacy. Polypharmacy was associated with having supplemental private health insurance and higher health care utilization (Kim et al., 2014) and seeking a greater number of different health providers (Chan et al., 2009). Place of residence (urban and metropolitan areas) was also an independent predictor of polypharmacy (Chan et al., 2009; Jiménez Herrera & Fernández Rojas, 2008). These findings suggest that characteristics at the community and the health system's levels may play an independent role in determining polypharmacy

1.2.7 Community-Level Determinants of Polypharmacy

At the community (area) level,[3] the findings from the geographic variation studies (Table 1.3) were similar to the individual-level determinants described above (Tables 1.1 and 1.2). Communities with higher concentration of older adults (Hovstadius, Astrand, et al., 2010; Perry & Turner, 2001), with lower levels of health status (Cashion et al., 2015; Franchi et al., 2013; Hovstadius, Astrand, et al., 2010), and where a higher percentage of individuals were women (Cashion et al., 2015; Perry & Turner, 2001) tended to have greater polypharmacy. Most studies that investigated community-level characteristics utilized aggregated data only. Therefore, this evidence could simply reflect the aggregated experiences of the individuals living in a community.

In addition, communities with higher income and education levels (Cashion et al., 2015; Perry & Turner, 2001) tended to have higher polypharmacy – although one study found that communities with higher education levels tended to have lower polypharmacy (Hovstadius, Astrand, et al., 2010). The instability of these and other factors suggests that other factors or pathways may be at play, and that studies that find these associations may be incomplete models of a more complex reality. When interpreting these findings is important to consider that these associations do not imply causation or underlying mechanisms.

[3] The Merriam-Webster dictionary defines a community as an "*interacting population of various kinds of individuals in a common location*" (https://www.merriam-webster.com/dictionary/community). In this study we use the term "community" interchangeably with "area" to refer to an individual's geographic area of residence.

1.2.8 Health Systems Determinants of Polypharmacy

The association between polypharmacy and health systems factors was unclear in the studies that we reviewed (Table 1.3). The main health system factor investigated was the utilization of medical care (doctor visits). One study found a strong correlation between greater number of medical visits and polypharmacy, independently from individual factors (Kim et al., 2014). Another study did not find an association between polypharmacy and greater utilization of medical visits when controlling for individual factors (Perry & Turner, 2001). The other health system characteristic examined was the number of doctors that worked in each area. Higher number of doctors was found to be correlated with lower polypharmacy (Hovstadius, Astrand, et al., 2010). We turn to the larger literature on geographic variation of health care utilization and health spending to identify the factors at the health system level that should be examined in order to better understand the supply-side drivers of polypharmacy.

1.2.9 Health Systems Determinants of Health Care Utilization

Significant geographic variations in health care utilization and spending have been demonstrated since the late 1960's (J. E. Wennberg, 2014; J. Wennberg & Gittelsohn, 1973). It has since become a consensus that geographic variations in health care utilization and spending are not entirely explained by population characteristics and underlying health needs (Medicine, 2013). Among older adults in the United States patient health status explained less than a third (29%) of area-level differences in total health spending (Zuckerman, Waidmann, Berenson, & Hadley, 2010). A study of patient preferences found that patient characteristics such as income and health explained 12% of the variation in spending; patient preferences explained an additional 5%. Added together, patient characteristics accounted for 17% of the variation (Baker, Bundorf, & Kessler, 2014).

Studies have found that supply-side factors explained a larger proportion of the geographic variation in health care utilization and spending (Cutler, Skinner, Stern, & Wennberg, 2013; J. E. Wennberg, 2014; J. Wennberg & Gittelsohn, 1973; Zuckerman et al., 2010). Health systems factors such as the number of physicians, physician specialty, and number of hospital beds explained 23% of the variation in health care spending among Medicare

beneficiaries in the United States[4] (Baker et al., 2014). Physician characteristics alone (physician beliefs, preferences and prescription patterns) explained 17% of variation in health spending in Medicare (Cutler et al., 2013). Physician mix (the type of specialty) was found to be independently associated with service utilization, indicating patterns of supply-induced demand (J. Wennberg & Gittelsohn, 1973). Type of health insurance plans were not found to be associated with health utilization and spending (Medicine, 2013).

A study of geographic variation in the use of psychiatric drugs in the United States found that 50-60% of the variation was explained by health systems factors: higher access to care (as measured by the number of physicians), higher insurance coverage, and pharmaceutical marketing efforts (as measured by dollars spent in advertising) (King & Essick, 2013). Studies of other, non-polypharmacy forms of drug utilization may help shine a light on what may be the relevant health systems factors that should be considered when investigating the determinants of polypharmacy.

In addition, geographic variation analyses of non-polypharmacy health outcomes indicate that there is a lack of correlation between the availability of health services and underlying population health needs (J. Wennberg & Gittelsohn, 1973). There is also a lack of correlation between health services utilizations or expenditures and health outcomes (Medicine, 2013).

1.2.10 Prevalence and Determinants of Inappropriate Polypharmacy in Older Adults

Population-level studies have found that, as measured by the Beers Criteria, inappropriate drug utilization was present in 31.9% of older adults age 65 years and over in the United States (Texas) (Holmes, Luo, Kuo, Baillargeon, & Goodwin, 2013) As measured by clinically relevant drug-drug interactions, inappropriate drug utilization was present in 29% of older adults 75 years and over in Sweden (Johnell, Fastbom, Rosen, & Leimanis, 2007).

The main determinant of inappropriateness is the higher number of concomitant drugs. As measured by the Beers Criteria, the occurrence of inappropriateness among individuals 65 years and older in Texas was 2.5 times

[4] Medicare population: older adults age 65 and over, disabled individuals, and persons with chronic kidney disease.

greater among persons taking 6-8 drugs and 4.4 times greater among persons taking 9 or more drugs as compared to persons taking 1-5 drugs, all other things being equal (Holmes et al., 2013). As measured by clinically relevant drug-drug interactions, the occurrence of inappropriateness among individuals age 75 years and older in Sweden was 4 times higher among persons taking 5-7 drugs and over 45 times higher among persons taking 11 or more drugs when compared to those taking 1-4 drugs (Johnell et al., 2007). Other factors such as higher age, female gender, low education levels, living alone, and higher number of physician visits have been independently associated with inappropriateness (Bongue et al., 2009).

1.3 CONTEXT

1.3.1 Rationale for Investigating Polypharmacy in Brazil

Few investigations have explored the occurrence of polypharmacy among older adults in LMICs. Polypharmacy may be an unrecognized problem in these countries.

Brazil presents a perfect storm for the occurrence of polypharmacy - its fast aging population has growing rates of chronic diseases, increasing the demand for medicines (A. Palloni & McEniry, 2007); its recent economic growth has led to rising income levels, increasing the ability to pay for medicines (Branco, 2010); several government programs have been put in place to expand access to generics (Dias & Romano-Lieber, 2006) and to provide medicines for those who cannot afford them (Secretaria de Políticas de Saúde, 2000); and people have increasingly resorted to judicial courts to request medicines not covered or not timely provided by government programs[5] (J. Biehl, Amon, Socal, & Petryna, 2012, 2016).

In fact, Brazil has become the sixth largest country-level pharmaceutical market in the world, as measured by total expenditures on drugs. At around US$ 200 per capita per year, Brazil has largest spending on drugs than countries such as China, which is the world's second country-level pharmaceutical market (Informatics, 2014).

[5] The growing phenomenon of "judicialization of health" has grown markedly in Brazil in the last decade. Individuals resort to courts to request access to medicines regardless of coverage by government formularies. Based on the constitutional right to health, judges grant virtually all drug requests, causing distortions to government policies and impacting public budgets (Vieira & Zucchi, 2007).

1.3.2 Prevalence and Determinants of Polypharmacy in Brazil

There have been several studies investigating drug utilization and polypharmacy among older adults in Brazil, producing various prevalence estimates (Table 1.4). It is possible that the difference between studies may be explained at least in part by differences in source populations and sampling mechanisms. However, some true differences may be present.

After we discuss the conflicting results from studies with various sampling mechanisms, below we reason that differences in polypharmacy rates estimated by two large population-based studies in Brazil may reflect true geographic variations. We hypothesize that this finding is likely to be explained by both demand- and supply side differences across areas, and we propose that further geographic variation analyses should be conducted in order to clarify the role of individual and geographic level factors in determining polypharmacy in Brazil.

When identifying and selecting a sample of individuals to participate in a survey, it is important to ensure that all eligible individuals have the same opportunity to participate, and that those who do participate are not systematically different from those who do not. Studies with non-random sampling mechanisms may have biased results. Selecting individuals who are systematically different from the general population may also introduce bias. Individuals who are part of health programs (Flores & Mengue, 2005; Mosegui, Rozenfeld, Veras, & Vianna, 1999), who live in the closer proximity to a health program (Marin et al., 2008), or who are healthier than the general population (Flores & Mengue, 2005; Mosegui et al., 1999; Torres Faggiani et al., 2007) may have systematically different factors determining their need and influencing access to polypharmacy as compared to the general population. Lastly, studies with very low sample sizes may have great levels of uncertainty around their estimates (Flores, 2005; Coelho-Filho, 2004; Torres-Fagiani, 2007; Marin, 2008).

From the studies below (Table 1.4) it seems that studies that selected individuals in a non-randomize), studies that explicitly selected healthier individuals, and studies that selected individuals with greater access to care tended to find higher rates of polypharmacy than studies of the overall population (the highest rates of polypharmacy were estimated in these studies = 38.2% in Mosegui, 1999 and 27% in Flores, 2005; and the

fourth highest rate as well = 25.2% in Marin, 2008). Studies with very low sample sizes did have great levels of uncertainty around their estimates (Coelho Filho, Marcopito, & Castelo, 2004; Flores & Mengue, 2005; Marin et al., 2008; Torres Faggiani et al., 2007).

In our assessment, only two of the reviewed studies were likely to have adequately estimated the prevalence of polypharmacy in the general population (Loyola Filho, Uchoa, Firmo Jde, & Lima-Costa, 2005; Loyola Filho, Uchoa, & Lima-Costa, 2006). These studies are highlighted in grey on Table 1.4 and have strikingly different prevalence estimates.

Each of these studies examined the population of older adults aged 60 and over in a different Brazilian municipality. The two municipalities were located in the same state, about a mere 170 miles apart. While one of the studies implemented a multi-stage sampling process to ensure that its sample was representative of all older adults in the municipality (Loyola Filho et al., 2006), the other examined all persons aged 60 and over in the area (Loyola Filho et al., 2005).

In the municipality with a large and predominantly urban population, the prevalence of polypharmacy among persons 60 years old and over was 14.3% in 2003 (Loyola Filho et al., 2006). In the municipality with the smaller and predominantly rural population, the prevalence of polypharmacy among persons 60 years old and over was 25.5% in 1997 (Loyola Filho et al., 2005).

It is likely that the estimates reflect true differences in the prevalence of polypharmacy across geographic areas in Brazil. This finding poses a small-area-variation problem similar to differences in health service utilization identified in other settings (J. Wennberg & Gittelsohn, 1973). The expansive literature on geographic variation analyses of health care utilization[6] indicates that most of the variation across areas tends to be explained by differences in supply-side factors such as physicians' preferences and prescription patterns. These factors should be further investigated in the Brazilian context.

There is only one study that explored geographic variation in polypharmacy in Brazil (Coelho Filho et al., 2004). This study analyzed three districts of a main Brazilian metropolitan area (Fortaleza, CE), selected

[6] A review of this literature is provided in earlier sections.

according to their income levels. The study found that the prevalence of polypharmacy was correlated with higher area-level income. However, the study did not control for other individual and area-level characteristics that may also affect polypharmacy.

The individual-level factors that have been associated with polypharmacy in the Brazilian context have in general been similar to those identified in international studies: female gender, higher age, higher levels of chronic diseases, and higher access to health services (Carvalho, Pascom, Souza-Junior, Damacena, & Szwarcwald, 2005; Loyola Filho et al., 2005; Loyola Filho et al., 2006). There is uncertainty surrounding some characteristics such as marital status – polypharmacy was found to be more frequent among married individuals (Loyola Filho et al., 2006) but also among non-married individuals (Loyola Filho, Firmo, Uchoa, & Lima-Costa, 2011) in different studies. Similarly, polypharmacy has been associated with higher (Loyola Filho et al., 2011) and lower (Carvalho et al., 2005) schooling and income levels.

Investigations that address a wide set of individual characteristics, and that assess the role of geographic-area factors while controlling for individual factors are greatly needed in order to further elucidate the determinants of polypharmacy in Brazil.

Table 1.4 Prevalence of polypharmacy among non-institutionalized older adults in Brazil

Author, Year	Year of data collection	Setting	Study Population	% Polypharmacy
Mosegui 1999	1996	Rio de Janeiro, RJ	Convenience sample of "University for Seniors" members with regular medical and pharmaceutical care. Women only. N=634	38.2%
Loyola-Filho 2005	1997	Bambuí, MG	Total population of seniors living in the municipality N=1606	25.5%
Flores 2005	2001-2002	Porto Alegre, RS	Random sample of not-bedridden, able-to-inform seniors enrolled in a hospital-associated community health program N=215	27%
Loyola-Filho 2006	2003	Belo Horizonte, MG	Two-stage cluster random sample of seniors living in a metropolitan area N=1598	14.3%
Coelho-Filho 2004	2003	Fortaleza, CE	Multistage systematic sample of seniors living in three districts of different socio-economic status N=668	8.9%
Torres	2006	Porto	Simple random sample of non-disabled	18.3%

Fagiani 2007		Alegre, RS	seniors living in the city N=480	
Marin 2008	2007	Marília, SP	Simple random sample of seniors living in the catchment area of a family health program N=301	22.6%

Note: Studies are presented in order of publication. All studies investigated individuals aged 60 years and over living in the community. All studies defined polypharmacy as the use of five or more medicines. Additional selection criteria were listed accordingly. N=number of people included in the study. Setting indicated by city, state. Polypharmacy defined as daily intake of five or more medicines. All studies were cross-sectional surveys. Data collection conducted by in-person interviews unless noted otherwise.

1.3.3 Access to Medicines in the Brazilian Health System

The Brazilian Unified Health Care System (*Sistema Unico de Saude - SUS*), created in 1988, covers the entire population, including the elderly. The system is mostly funded by taxation. The public health system provides comprehensive health care free of charge for the population, including medicines.

The public health system it is the sole source of care for over 75% of the Brazilian population. About 24% of the population – mostly the employed and those financially better off – have supplementary private health insurance (Viacava, Souza-Junior, & Szwarcwald, 2005). Private health insurance provides access to private networks of hospitals and health providers that would otherwise be accessible only out-of-pocket. Private services typically offer faster access than in the public system.

Private health insurance does not cover drugs for outpatient use in Brazil. Medicines must be purchased out-of-pocket in private pharmacies. By regulation most "prescription" drugs can be purchased in the private market without a medical prescription. This includes most drugs to treat chronic diseases. Mental health treatments and controlled substances such as and antimicrobial agents are the exception, and their sales are strictly monitored.

Drug provision in the public health system is limited to a national formulary. States, federal and local governments share the responsibilities of drug provision according to a tiered system. Cheaper medicines that treat common conditions belong to the “essential” or “basic” formulary and are supplied by municipalities. Higher-cost drugs that are used in more restricted situations are part of the “specialized” formulary and are supplied by states, with federal funding. Drugs to treat "strategic" conditions (public health priorities such as

HIV) are supplied by the federal government. (Secretaria de Políticas de Saúde, 2000). Drugs provided in the public system are dispensed only in public pharmacies and typically require medical prescriptions that must be current and must be issued by a public health service.

Brazil has strong policies to increase access to medicines and reduce drug prices. Policies to incentivize the production of generic drugs were shown to have significantly reduced overall drug prices (Vieira & Zucchi, 2006). Government programs also subsidize drugs to treat chronic diseases such as hypertension and diabetes that can be purchased at great discounts in participating private pharmacies (Pinto, Miranda, Emmerick, Costa, & Castro, 2010). In addition, based on the right to health established by the 1988 Constitution, individuals have increasingly used legal action against the government in order to obtain drugs that are either not part of government formularies or not provided in a timely or sustainable manner (J. Biehl, Socal, & Amon, 2016). These judicial pathways have further expanded access to medicines in the country in recent years.

1.3.4 Sao Paulo - Population and Geographic Characteristics

The city of Sao Paulo is a megalopolis of country-size proportions. Because of its large population, its administrative structure, and the heterogeneity across each of its areas, Sao Paulo provides one of the best settings in which to investigate the occurrence and the determinants of polypharmacy in Brazil.

With about 12 million inhabitants Sao Paulo is the largest city in Brazil and one of the five largest cities in the world. If Sao Paulo were a country, it would represent the world's 77th largest population, ahead of countries such as Belgium, Portugal, Greece, Sweden and Bolivia (Factbook, 2010). Sao Paulo is the most important business and financial center of Brazil and likely of the Southern Hemisphere. Sao Paulo generates 12% of the Brazilian GDP alone (Ribeiro, 2012). The city of Sao Paulo has a central government and is administratively divided into 31 sub-prefectures (Municipal Law nr. 13,399 of August 01, 2002) (Figure 1.1).

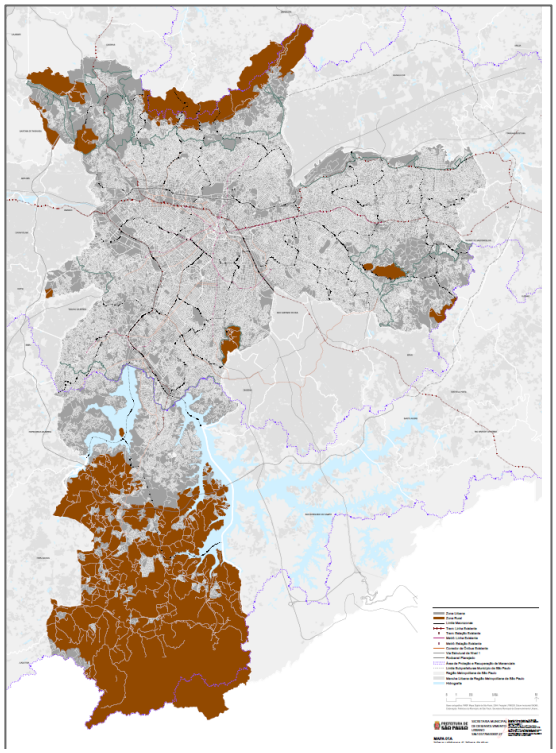
Figure 1.1 Administrative Divisions of the City of Sao Paulo

Source: Municipal Planning Secretariat of the City of Sao Paulo (SEMPLA)

Each sub-prefecture has their own administration, which is responsible for all public works such as road maintenance, sanitation, and others. The provision of health services in the public health system is overseen by the central administration and managed locally by the sub-prefectures (Paulo & Pública, 2011). Sub-prefectures also have some role in the private health system, as they may issue commercial licenses for health facilities and pharmacies independently from the central administration.

The demographic and socio-economic characteristics of Sao Paulo's 31 sub-prefectures vary widely. While the more centrally located areas are densely populated and heavily urban, there are peripheral areas that have almost rural characteristics, such as large territories and smaller and more scattered populations. Figure 1.2 displays the rural and urban characteristics of the city of Sao Paulo.

Figure 1.2 Rural and urban characteristics of the city of Sao Paulo



Note: brown-shaded areas represent areas with predominantly rural characteristics. Grey-shaded areas represent areas with predominantly urban characteristics. Lighter grey represents higher urbanization. Source: gestaourbana.prefeitura.sp.gov.br

Socio-economic status and housing conditions vary significantly across the areas. An index of socio-economic status incorporating education, income, and the composition of households was developed by the city's administration in order to identify the socio-economic differences across the multiple geographic areas (Paulo & Pública, 2011). The index was used to classify areas between predominantly poor, areas transitioning into middle class, areas predominantly of middle class, and areas predominantly rich.

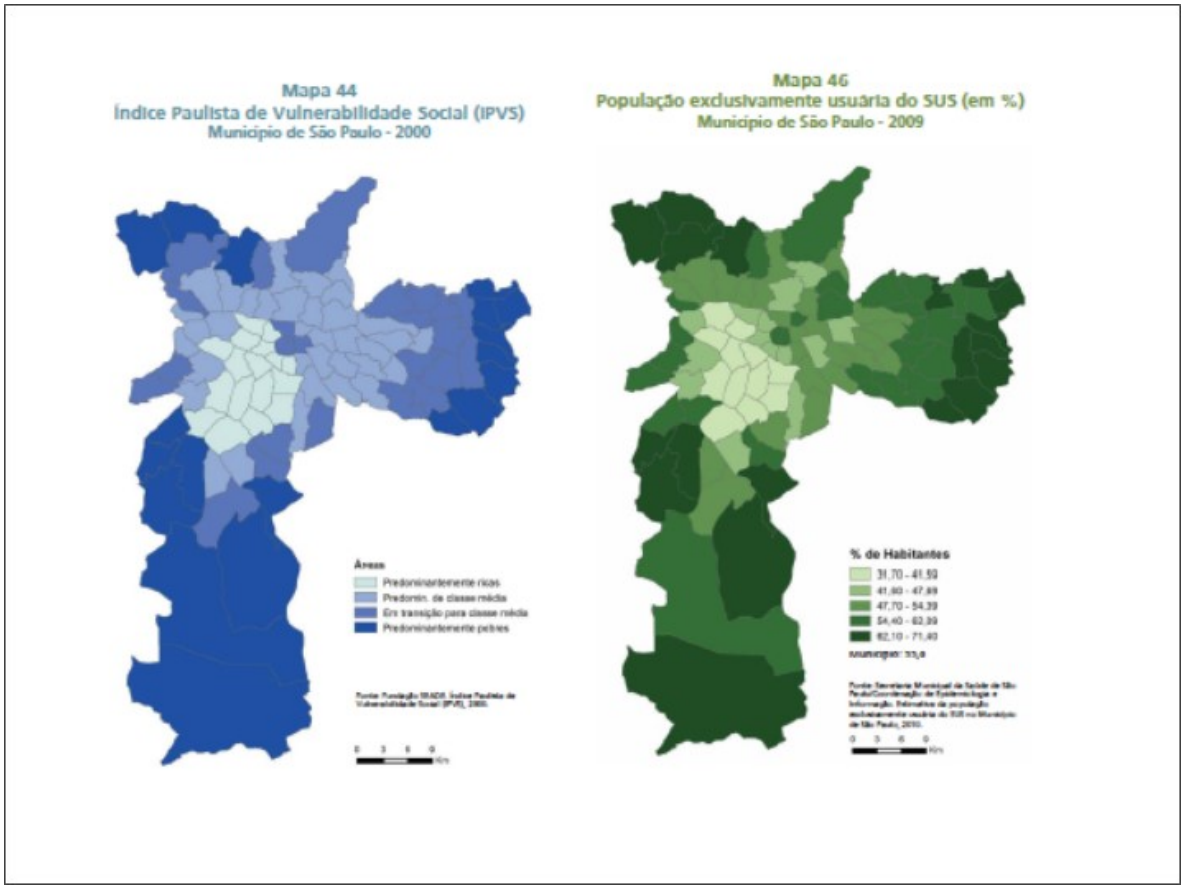
Figure 1.3 displays the distribution of the socio-economic index across the multiple geographic areas of Sao Paulo (darker colors indicate lower socio-economic status). In 2000, an estimated 28.9% of the population lived in predominantly poor areas; 31.1% lived in areas transitioning into the middle class; 28.6% lived in predominantly middle class areas; and 11.4% lived in predominantly rich areas (Paulo & Pública, 2011).

Most individuals who live in predominantly poor areas or in areas transitioning into middle class rely exclusively on the public health system to obtain their care. In other words, most individuals living in predominantly poor areas or in areas transitioning into middle class do not have private insurance coverage. The

average rate of depending exclusively on the public health system across the city of Sao Paulo was 55.6% in 2009 (Paulo & Pública, 2011). This was lower than the Brazilian average of about 76% in 2003 (Viacava et al., 2005).

There is a great overlap between having private health insurance coverage and living in predominantly middle class or rich areas. Up to 70% of residents of predominantly rich areas have private health insurance. In predominantly poor areas a maximum of 30% of residents have private health insurance (Figure 1.3) (Paulo & Pública, 2011).

Figure 1.3 Socio-economic status (left) and private insurance coverage (right) in Sao Paulo



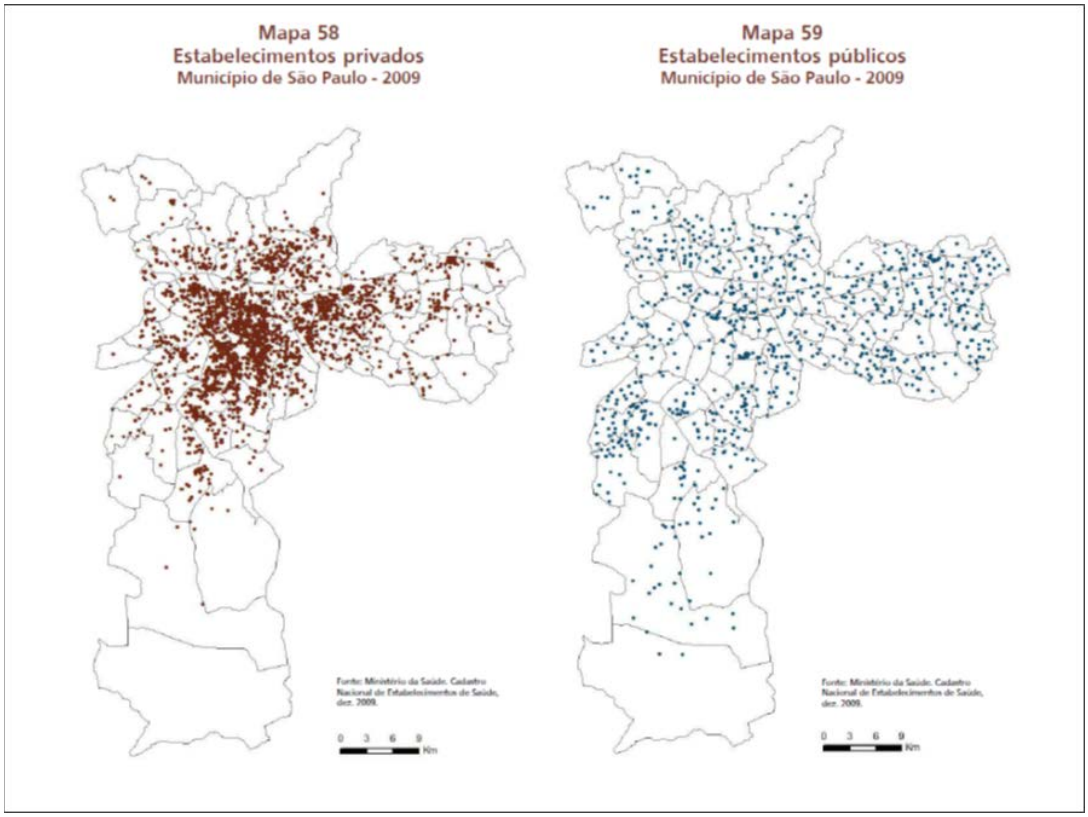
Note: Darker colors reflect worse conditions: lower socio-economic status (left) and lower health insurance coverage (right). Source: Atlas Sao Paulo, 2012.

1.3.5 Sao Paulo – Health System Characteristics

The largest proportion of health services in Sao Paulo is part of the private sector (91%, or 10,641 out of 11,653 health services). Around 93% of the private health services are medical and dental clinics. The public health system maintains 818 primary care facilities (basic health units and outpatient clinics) and 86 hospitals, as well as other health facilities such as diagnostic laboratories and others. There are 219 hospitals in Sao Paulo, with about 35,000 beds. About 50% of the total hospital beds are available to the public health system, either directly or via contracts. However, only about 5% of the equipment for diagnostic imaging, 1.4% of the equipment for life support and 2.4% of the equipment for dental care is available to the public health system. The health workforce in Sao Paulo is composed of about 130,000 health professionals, of which over 28,000 are physicians. The public health system employs over 50,000 workers, of which over 8,000 are physicians and 12,000 are nurses (Paulo & Pública, 2011).

There is great heterogeneity in the distribution of health services across the Sao Paulo sub-prefectures. Private health services are highly concentrated in the central areas of the city. The distribution of private health services greatly overlaps with areas of higher socio-economic status and greater private health insurance coverage (Figure 1.4). The distribution of the public health services is less centralized and less correlated with area-level socio-economic status. The implementation of public health services has been at least to some extent intended to cover underserved areas with greater population health needs. Of the 115 primary care clinics opened between 2005 and 2008 in Sao Paulo, the majority (51%, 59 clinics) was allocated to high need areas; other 45% (52 clinics) were allocated to medium-need areas, and only 4 clinics (3.5%) were allocated to areas with low need (Figure 1.4) (Paulo & Pública, 2011).

Figure 1.4 Distribution of private (left) and public health services (right) in Sao Paulo



Source: Atlas Sao Paulo, 2012.

1.4 STUDY OBJECTIVES

1.4.1 Overall Research Goal

This study aims to contribute to the understanding of the phenomenon of polypharmacy among older adults in Brazil. Specifically, we aim to quantify and characterize the occurrence of polypharmacy and identify its risks (as measured by the occurrence of inappropriate polypharmacy) and its determinants.

The ultimate goal of this research is to provide useful information to policy-makers that may want to understand whether polypharmacy is necessarily a problem among Brazilian older adults; what is the extent of the problem; and what are the main factors at the individual-, the community-, and at the health system level that may contribute to the occurrence of polypharmacy in this population.

Policy makers need information that truly reflects the realities of the populations that they aim to serve. There is still a dearth of evidence with polypharmacy in Brazil. Specifically, its association with inappropriateness, and therefore its potential health risks, its time trends, and its community- and health systems determinants, are not yet fully understood.

Particularities of access to medicines in the Brazilian context – private insurance plans not covering outpatient drugs; private purchase of prescription drugs not requiring official prescriptions; thriving governmental programs and policies to expand access to medicines; and the possibility of obtaining medicines through judicial pathways – suggest that findings from studies conducted elsewhere may not be generalizable to Brazil.

1.4.2 Specific Research Aims

Aim 1: To quantify and characterize the occurrence of polypharmacy among the Sao Paulo older adult population

Sub-aims:

1a. To measure the overall prevalence of polypharmacy in adults aged 60 years old and over in Sao Paulo in the years 2000, 2006 and 2010

- To quantify which proportion of older adults are exposed to polypharmacy in each of the studied years
- To identify differences over time in the occurrence of polypharmacy among the population of older adults

1b. To quantify the occurrence of inappropriate polypharmacy among those with polypharmacy, measuring:

- The types of risk,
- The levels of risk, and
- Differences over time

1c. To identify which drug classes are most often part of polypharmacy regimens and which drugs or drug combinations are most frequently associated with drug risk

Aim 2: To identify individual- and community-level factors associated with polypharmacy and inappropriate polypharmacy in the Sao Paulo older adult population

Sub-aims:

2a. To document area-level variations in the prevalence of polypharmacy and inappropriate polypharmacy among the Sao Paulo older adult population

2b. To analyze the association between polypharmacy and individual-level characteristics, as well as inappropriate polypharmacy and individual-level characteristics,

2c. To analyze the association between polypharmacy and community-level characteristics, controlling for individual-level factors; and the association between inappropriate polypharmacy and community-level characteristics, controlling for individual-level factors

Aim 3: To identify health systems factors associated with polypharmacy in the Sao Paulo older adult population

Sub-aims:

3a. To analyze the association between polypharmacy and health systems characteristics, controlling for individual and community-level factors

3b. To quantify the extent to which health systems factors contribute to explaining geographic variations in polypharmacy in addition to the variation explained by individual- and community-level factors.

Note

It is important to mention that the cross-sectional structure of this study does not provide an adequate setting to examine causative relationships between the multiple factors that we describe and polypharmacy. We some times call the factors associated with polypharmacy as "determinants" in this text, mostly when: 1) there is theoretical basis supporting potential causal pathways; 2) there is evidence from other studies supporting causal pathways; 3) the conceptual framework indicates causal pathways; or 4) the factors represent potential policy targets that should be further explored. We reason that the direction of the relationships goes from these factors to polypharmacy. However, we acknowledge that this may not always hold true. We review this rationale and the limitations in greater detail in Chapter 6.

Our findings are intended to help inform future research and identify potential policy targets for further exploration. The findings of this study will be specific to the Sao Paulo older adult population. In Chapter 6 we discuss the full set of limitations as well as the generalizability of our study. While our results may not be directly generalizable to other Brazilian settings, they may help inform future studies and comparative analyses.

1.5 CONCEPTUAL FRAMEWORK

We draw from the conceptual framework of Societal and Individual Determinants of Medical Care Utilization developed by Andersen & Newman (1973) (Figure 5) (R. Andersen & Newman, 1973). In our study the outcome of interest – "health service utilization" – is the use of polypharmacy.

Andersen and Newman's framework envisioned health services utilization as the result of a "sequence of conditions". At the individual level, the framework divided these conditions as predisposing conditions ("the predisposition of the individual to use services"), enabling conditions (the individual's "ability to secure services"), and illness level (the diagnoses, level of symptoms and disability perceived by the individual or ascertained by the health provider).

At a broader level the framework identified determinants at the societal and health system's levels. The model assumed that societal and health systems determinants affected service utilization only via modifications on individual-level determinants. The possibility that societal and health systems factors might affect health services utilization independently from individual behavior and characteristics was not described.

There are many alternative versions of the model, adapted to accommodate different levels of detail as well as different interconnections between the spheres of determinants. Of interest, one of the model's versions also developed in the 1970's included a set of population-level determinants that mirrored the individual-level conditions (Andersen, 1994). This version of the framework described population-level predisposing, enabling, and need (illness level) factors that affected health services utilization independently from their individual-level counterparts (Andersen, 1994). The set of population-level determinants described by Andersen corresponds to

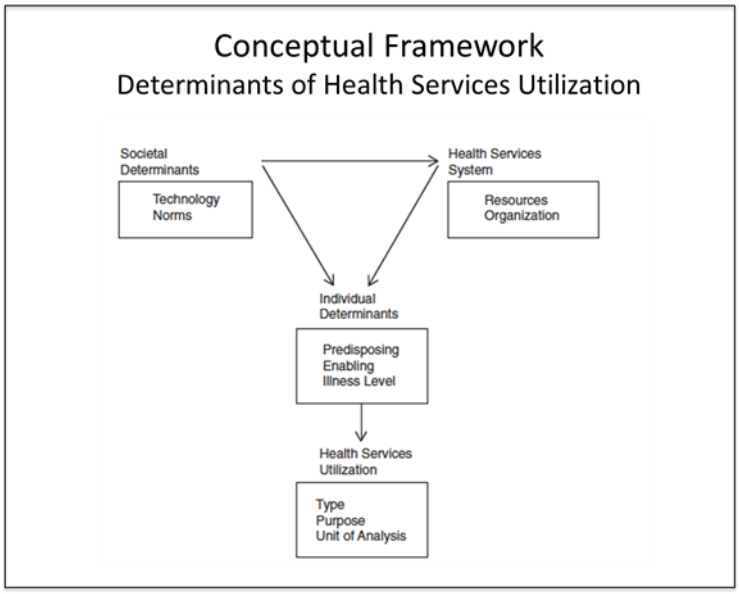
what in this study we called community-level determinants, and we will use the term "community determinants" to identify this set of factors in the conceptual framework.

In our study, we use the same conceptual model developed by Andersen. We adapt the graphic display of Andersen's conceptual model to, first, demonstrate that the type of service utilization (outcome) of interest in our study is polypharmacy. Second, we identify that polypharmacy may result in inappropriate polypharmacy. Third, we add a box to explicitly show the set of community determinants, divided in predisposing, enabling, and illness level. Fourth, we add solid arrows identifying the possible direct associations between community and health services system determinants and polypharmacy. Lastly, we use dashed arrows to identify the indirect associations between community and health services system determinants and polypharmacy that are mediated by individual-level factors (Figure 1.6).

We identify the main aims of this study in Figure 1.7. In Aim 1 we are interested in estimating the association between polypharmacy and inappropriate polypharmacy (solid line). In Aim 2 we are interested in estimating the associations between individual determinants and polypharmacy (solid arrow), as well as the association between community determinants and polypharmacy after controlling for individual-level characteristics (solid line). In Aim 3 we are interested in estimating the association between health systems determinants and polypharmacy after controlling for individual-level characteristics (solid line).

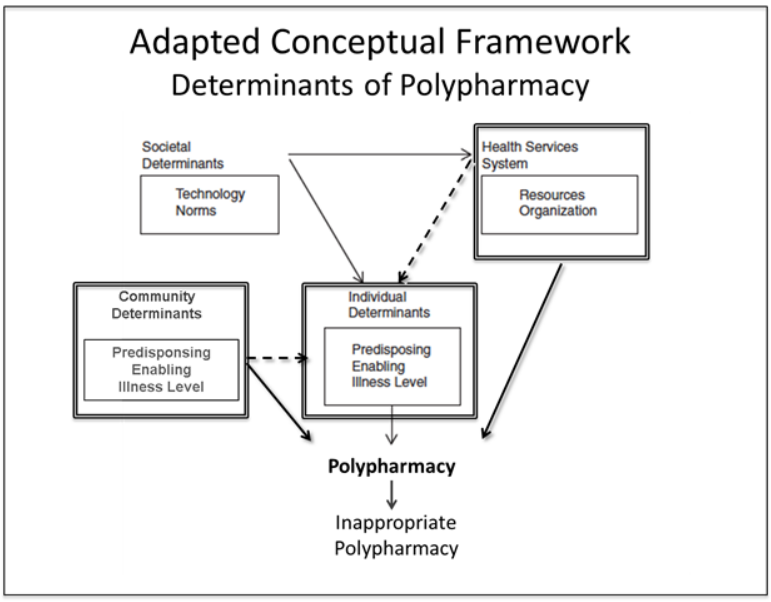
Because our analysis is limited to one single city we assume that societal determinants (technology and norms) are constant across areas. Examples of technology and norms of interest in the case of polypharmacy are pharmaceutical regulations, policies for access to medicines, and the types and brands of pharmaceuticals available in the market. These factors are fixed within the city of Sao Paulo, and so we do not estimate them in our models.

Figure 1.5 Andersen & Newman's societal and individual determinants of medical care utilization – Conceptual framework



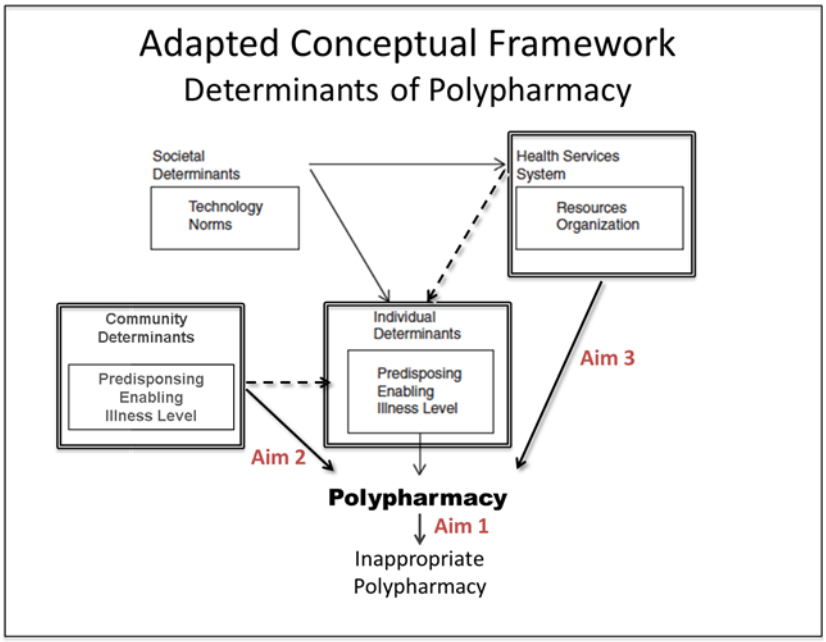
Source: Andersen & Newman (1973)

Figure 1.6 Adapted conceptual framework utilized in this study



Source: adapted from Andersen & Newman (1973), based on Andersen (1995). Individual, Community and Health Systems Determinants Are Identified by Thick Boxes

Figure 1.7 Adapted conceptual framework identifying the study aims



Source: adapted from Andersen & Newman (1973), based on Andersen (1995).

A potential limitation of the proposed conceptual framework is that it does not comprehend all the relevant dimensions of access to care (Penchansky & Thomas, 1981; Peters et al., 2008). Access to care has been described as the combination of multiple disaggregated dimensions: availability, accessibility, accommodation, affordability, and acceptability of services. These dimensions are important in order to qualify the access to the health care resources that we investigated at the community level. It is especially important in order to understand potential mechanisms that are specific to the public or to the private health care systems in Brazil. We discuss these factors in greater detail in Chapter 6. We recommend that future studies should investigate these dimensions of pharmaceutical access in the Brazilian context, as they are likely to provide potential policy targets through which to improve quality and appropriateness of drug utilization in Brazil.

2. CHAPTER II: DESCRIPTION OF THE DATA SOURCES

In this study we combine comprehensive information from older adults living in Sao Paulo with community and health systems characteristics of the Sao Paulo sub-prefectures. We use the same data sources for all three aims. The individual-level data was obtained through a household survey of older adults conducted in Sao Paulo in the years 2000, 2006 and 2010. Community and health systems information for each of the sub-prefectures was collected from publically available online databases or calculated from the survey data. Below we describe the data sources utilized in this study.

2.1 INDIVIDUAL LEVEL DATA – THE SABE STUDY

2.1.1 History and Motivation

The SABE study (*Saude, Bem Estar e Envelhecimento* – Health, Wellbeing and Aging) was a survey originally carried out to investigate health conditions of older adults in large metropolitan areas of six Latin American countries: Brazil (Sao Paulo), Argentina (Buenos Aires), Chile (Santiago), Uruguay (Montevideo), Mexico (Mexico City), Cuba (Havana) and Barbados (Bridgetown). The survey was modeled after the United States Health and Retirement Study (HSR). In order to allow for cross-country comparisons, the questionnaires and methodologies were standardized using the questions and methodology from the HSR.

A population-based multi-stage sampling framework was employed in order to ensure that the samples of individuals investigated in the SABE study were representative of the population of non-institutionalized older adults in each of the survey sites. A common questionnaire and standardized data collection procedures were adopted in order to facilitate cross-country comparisons. The methodology and findings from the SABE study were extensively published. A summary by the leading academic investigators provides an overview (A. Palloni & McEniry, 2007).

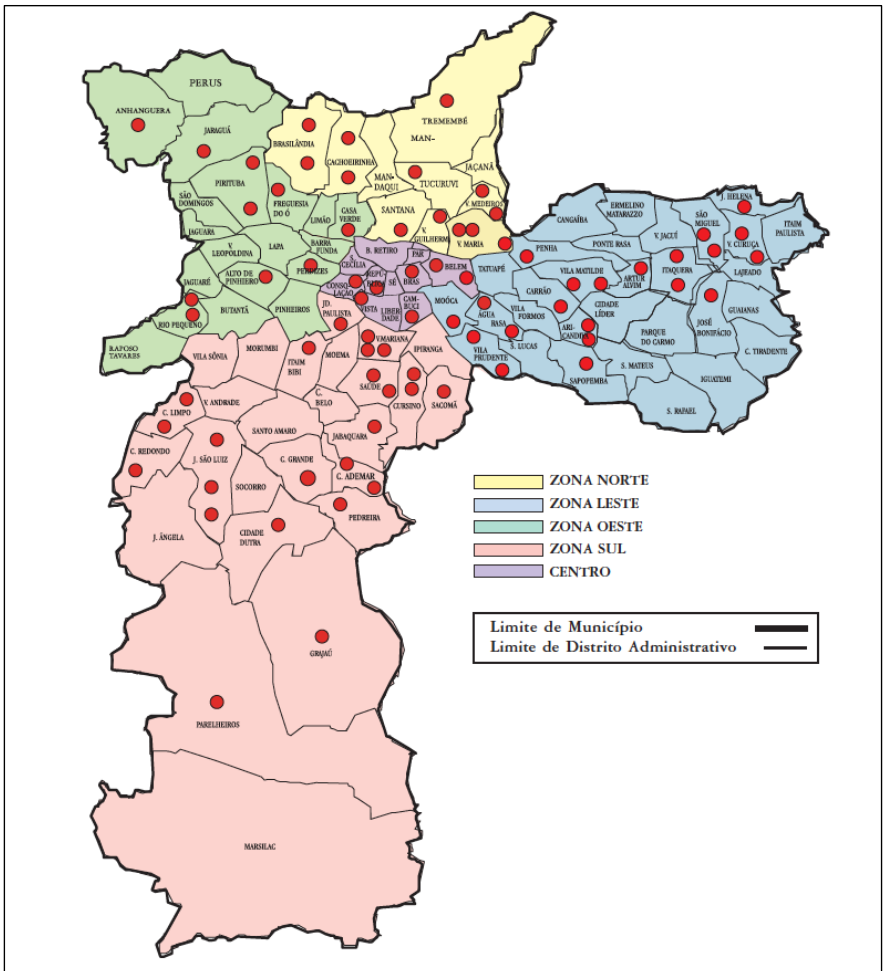
The SABE study was an initiative of the Pan-American Organization in partnership with academic institutions in each of the participating countries. Universidade de Sao Paulo (USP) was the academic institution that implemented the SABE study in Brazil.

Data collection in the original SABE study was conducted between 1999 and 2000. In Sao Paulo over 2,000 individuals were surveyed in their households. When participants were not able to inform the interviews were conducted with a proxy. The participants in the SABE study were distributed across most areas of the city of Sao Paulo (Figure 2.1).

In 2006 a USP initiative provided the resources for a new wave of data collection. An attempt was made to locate and re-interview all individuals who had participated in the original SABE study. In addition, new participants were sampled to ensure that the study sample was representative of the population of non-institutionalized older adults living in Sao Paulo in that period. Another wave of data collection repeating the same methodological structure was carried out in 2010. The survey questionnaire underwent minor modifications across the survey years.

Whereas data from the first wave of the SABE study is publicly available (Inter-university Consortium for Political and Social Research) the two other waves of data are proprietary of USP. The SABE data included in the present study was obtained from USP and was utilized with their permission.

Figure 2.1 Distribution of SABE participants across the Sao Paulo geographic areas



Note: Red dots identify areas with at least one observation in the original SABE study. Source: Palloni, 2000.

2.1.2 Sampling Method

The sampling process of the SABE survey in Sao Paulo was conducted in two stages. In the first stage, census tracts (primary sampling units) were selected from the 1996 Census master sampling frame. In this stage the probability of selection for each census tract was equal to its total number of households. Because each sub-prefecture contained thousands of census tracts, the probability of selection was fairly random at the sub-prefecture level.

In the second stage, the census tracts were stratified according to the proportion of the heads of households who were illiterate. Within each stratum households were selected with equal probability (secondary sampling units). All persons over 60 years of age living in the household were invited to participate, including participants'

spouses. The study oversampled individuals above 75 years of age, selecting them through a separate, equal-probability sampling process (Alberto Palloni & Peláez, 2000). When weighted by inverse selection probability weights, the final sample of the SABE survey is representative of the non-institutionalized population aged 60 years and older living in the city of Sao Paulo in each year.

2.1.3 Overview of Waves and Participants

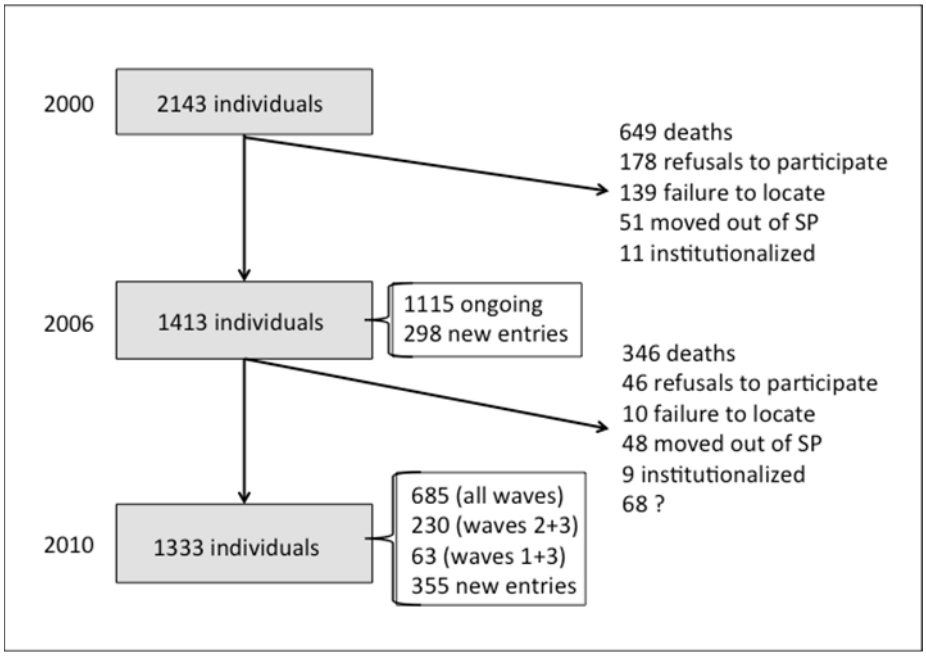
The final sample of the SABE survey constituted of 2,143 participants in 2000, 1,413 participants in 2006 and 1,333 participants in 2010. Out of the total 4,889 interviews conducted in the SABE study, 903 (18%) were carried out with a proxy. The total 4,889 interviews covered 3,777 different households. On average 1.78 individuals participated per household. Overall 67.2% of households (n=2538) contributed with only one participant, and 96.9% of households (n=3661) contributed up to three participants. Less than 5% of the households contributed four or more participants. The maximum number of participants per household was 10 in 2000, 7 in 2006 and 4 in 2010.

Out of the total 4,889 participations in the SABE study 2,796 (57%) individuals participated in only one wave; 1,408 (29%) participated in two waves; and 685 (14%) participated in the three survey waves.

Death was the major reason why some individuals from the first wave were not reexamined in the second. At the second wave of data collection, in 2006, 1,115 individuals from the original cohort were reexamined, and 298 new participants were included. Out of the 1,028 individuals without a follow-up, 649 (63%) had died. Other 178 (17%) refused to participate, 139 (14%) were not located, 51 (5%) had moved out of Sao Paulo and 11 (1%) had been institutionalized. At the third wave of data collection, in 2010, a new 355 individuals were examined. Other 430 members of the original cohort and 68 members of the second cohort were not reexamined in 2010, largely due to the same causes (Figure 2.2).

The addition of new participants in each wave was implemented in order to ensure that the final sample in each wave was representative of the Sao Paulo older adult population when survey weights were applied to reconstruct the population.

Figure 2.2 The Sao Paulo SABE study – Participants and follow-up



Source: Sao Paulo SABE database

Because each sub-prefecture has thousands of census tracts, the likelihood of selection of each specific sub-prefecture is fairly random. The selected SABE participants were distributed across 27 of the 31 sub-prefectures in 2000; 30 sub-prefectures in 2006; and 30 sub-prefectures in 2010 (Table 2.1).

One of Sao Paulo sub-prefectures (Cidade Tiradentes) was not represented in any of the SABE study samples. Three sub-prefectures were not represented in 2000 but were represented in 2006 and 2010 (Ermelino Mattarazzo, Guaianases and Sao Mateus). Because our study depended on characteristics measured at the individual level, areas that had no participants were not included in our analyses.

Each sub-prefecture that was represented in the SABE sample had on average 108 participants in 2000 (the minimum number of participants per area was 13 and the maximum was 182). In 2006, each sub-prefecture had on average 63.8 participants (minimum 5 and maximum 111 participants per area). In 2010, each sub-prefecture had on average 56.8 participants (minimum 4 and maximum 105) (Table 2.1).

Table 2.1 Overview of SABE participants

	2000	2006	2010
Nr. of Areas	27	30	30
Nr. participants	2,143	1,413	1,133
Participants per Area			
Avg (sd)	107.7 (48.5)	63.8 (26.2)	56.8 (21.7)
Min–max	13–182	5–111	4–105

Source: Sao Paulo SABE database

2.1.4 Data Collection and Variables

The SABE study collected comprehensive information on participants' demographic and socio-economic characteristics, current and past health conditions, and ongoing treatments. Most information was collected by self-report. Table 6 describes the individual-level characteristics collected in the SABE study that we will use in this analysis.

Information on medicine use was collected via self-report and researchers directly checked pill bottles, cartons and blisters to confirm the information provided by the participant (Landry, 1988). All pharmaceutical products, including over-the-counter, herbal and homeopathic drugs, were recorded. Information on drug dosage or number of intakes a day was not collected.

The SABE study recorded medicines using the Anatomical Therapeutic Chemical classification (ATC) developed by the World Health Organization (WHO). The WHO-ATC classification aims to operationalize drug utilization research and provide a "standard language" for "exchanging and comparing data on drug use at international, national or local levels" (WHO Collaborating Centre for Drug Statistics Methodology).

The WHO-ATC classification indexes active ingredients of allopathic drugs using alphanumeric codes. In this classification, the drugs are first divided according to the organ or system in which they act (level 1), and then they are progressively subdivided according to therapeutic subgroup (level 2), pharmacological subgroup (level 3), and chemical subgroup (level 4). The final level (level 5) identifies the specific drug (WHO Collaborating Centre for Drug Statistics Methodology). The WHO-ATC classification does not include products such as

herbal and homeopathic preparations. In Chapter 3 we provide a more detailed description of the WHO-ATC classification including an example.

We utilized the drug use information collected by the SABE study to generate two variables: polypharmacy, which we defined as the use of five or more drugs per day, and inappropriate polypharmacy, which we described as taking five or more drugs per day plus having at least one drug risk criterion. We identified each drug by its ATC code. In this investigation we focus on prescription and over-the-counter drugs only.

We assessed drug risk in the SABE sample using three different tools: the Beers Criteria, to capture potentially inappropriate prescribing (American Geriatrics Society Beers Criteria Update Expert, 2012), the ARS scale, to capture anticholinergic adverse effects (Rudolph et al., 2008), and the Hines list to capture clinically relevant drug-drug interactions (Hines & Murphy, 2011). A person was considered as having inappropriate polypharmacy if they were using five or more prescription or over-the-counter drugs per day, and had at least one positive criterion for drug risk in any of these three tools. A more detailed description of each tool, as well as the methodology that we used for their implementation, are provided in Chapter 3.

2.1.5 Main Covariates

Demographic characteristics collected included age, gender, marital status (binary coded as married or in a civil union versus single, widowed or divorced), race (binary coded as white versus other), and religion (binary coded as catholic versus other). Socio-economic characteristics included years of schooling (number of school years completed; repeated grades were not considered), number of people who lived in the household, having children who were still alive (yes, no), having a caregiver (yes, no), and per capita income. Income was measured in Brazilian Reais. Participants were asked to inform their total income per month from all different sources (wages, investments, pensions, rent, remittances, etc.). Per capita monthly income was calculated by dividing the total reported income by the number of people that depended on the income as informed by the participants.

Health care utilization characteristics included health insurance coverage status (having or not having private health insurance), number of physician visits in the last 12 months, and whether the participant underwent a preventative exam (mammogram for women and prostate exam for men) in the last 24 months. Health status

characteristics included presence and type of chronic conditions, presence and type of symptoms, level of disability, and self-reported health status[7]. Information on chronic disease was obtained by asking participants if they were ever diagnosed by a doctor or nurse with one or more of the following conditions: hypertension, diabetes, heart disease, lung disease, stroke, neuropsychiatric disorders, cancer, osteoporosis, and arthritis. Positive responses were aggregated to obtain the number of chronic diseases reported by each participant.

Information on symptoms was obtained by asking participants whether they experienced any of the following symptoms in the last 12 months: persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo, tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence. Positive responses were aggregated to obtain the number of symptoms reported by each participant.

Information on disability was obtained by asking participants whether they had difficulties performing one or more activities of daily living: walking across a room, getting dressed, bathing, feeding, transferring to/from bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores. Positive responses were aggregated to obtain the level of disability reported by each participant. Self-reported health status was obtained by asking participants how they assessed their current health. Participants could choose from the following options: excellent, very good, good, regular, bad, or very bad health. The information provided by the participants was aggregated to create a binary variable "good" (excellent, very good, or good) versus "bad" (regular, bad or very bad) health status.

Health behavior characteristics included smoking, alcohol, and self-medication habits. Smoking was classified as currently smoking versus not currently smoking. Alcohol use was classified as current alcohol use versus no current alcohol use. Self-medication information was obtained by asking who had issued the prescription for each of the drugs that a participant was using. If any of the drugs been started by the participant on their own will, or on recommendation from family members/ friends, without a prescription issued by a health provider, the information was recorded as self-medication. If all drugs were prescribed by a health professional, or if the person did not take any drugs, the information was recorded as no self-medication.

[7] Some characteristics, especially clinical symptoms and health care utilization, may have been influenced by polypharmacy. We make considerations about this possibility in greater detail in Chapter 6.

Table 2.2 Selected individual-level characteristics from the SABE study: Variable type and definition

Variable	Type	N	Definition
Drug Utilization			
Medicines	count	4889	Number of prescriptions and over-the-count drugs in use Medicines were coded using the WHO-ATC classification
Polypharmacy	binary	4889	Five or more prescription or over-the-counter drugs per day. Reference: zero to 4 drugs.
Inappropriate Polypharmacy	binary	4889	Five or more prescription or over-the-counter drugs per day, with at least one positive drug risk criterion[8]. Reference: any number of drugs with no risk criterion.
Excessive Polypharmacy	binary	4889	Ten or more prescription or over-the-counter drugs per day. Reference: zero to 4 drugs.
Socio-Demographic			
Age	count	4889	In years
Gender	binary	4889	Reference: males
Marital status	binary	4870	Married or in a civil union; reference: single, widowed or divorced
Income	continuous	4258	In Brazilian Reais (R$). Income from multiple sources (pensions, investments, wages, and others) was recorded. Per capita income was calculated by dividing the total reported income by the number of people that depended on the income as informed by the participants.
Health Insurance	binary	4886	Having private health insurance; reference: not having
Health Status			
Chronic Diseases	count	4889	Self-reported information on ever having been diagnosed by a doctor or nurse with one or more of the following conditions: hypertension, diabetes, heart disease, lung disease, stroke, cancer, psychiatric conditions, joint diseases, or osteoporosis.
Level of symptoms	count	4887	Self-reported information on having experienced persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo, tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence in the last 12 months.
Level of disability	count	4888	Self-reported information on having difficulty performing one or more activities of daily living: walking across a room, getting dressed, bathing, feeding, transferring to/from bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores.
Health Utilization			
Medical visits	count	4484	Self-reported information of the number of medical visits in the last 12 months.

[8] Drug risk criteria: Beers Criteria, Anticholinergic Risk Scale, and Hines list of clinically relevant drug-drug interactions. We describe these in more detail in Chapter III.

Preventative exam	binary	4609	Self-reported information on having undergone a preventative exam in the last 24 months. Mammogram for women or prostate exam for men. Reference group: no preventative exam.
Behaviors			
Smoking	binary	4887	Reference: not currently smoking
Alcohol	binary	4884	Reference: no current use of alcohol

Source: SABE Study.

Missing values were not a major problem in the SABE study. The characteristic with the most missing values was income, with 13% (n=631) missing values. The number of medical visits in the last 12 months was the second most frequently missing variable, with about 8% (n=406) of missingness. Having a preventative exam was the third with about 6% of missing values (n=280). All other variables had less than 5% missing values.

In our analysis, we excluded individuals with missing information for any variable, except for the three variables with most missing values that we described above (income, medical visits in the last 12 months, and preventative care in the last 24 months). We dealt with missing values differently for each of these three variables. For individuals with missing income information (n=631; 13%) we imputed the average per capita income for the corresponding gender and year. We identified individuals with imputed values by an indicator variable that represented missing income. No association between polypharmacy and missing income was found across the multiple analyses.

There were 348 individuals with missing values for medical visits in the last 12 months in 2000 (representing 16% of the 2000 sample). Because the large number of missing values allowed us to check for a relationship between missingness and the outcome, we identified missing individuals in the 2000 sample by an indicator variable for missingness and included in them in the 2000 analyses. Because in the other waves the number of missing individuals was too low, it did not allow us to check for a relationship between missingness and the outcome, and so we dropped these individuals from the analyses. In 2000, missing information on medical visits was associated with 64% lower odds of polypharmacy ($p<0.05$) in that year. We discuss this finding in chapter 4. Individuals with missing values for medical visits in the last 12 months in 2006 (N=54, 3.8% of the 2006 sample) and 2010 (N=4, 0.3% of the 2000 sample) were not included in the regressions.

There were 263 individuals (representing 19.7% of the 2010 sample) with missing values for preventative care in the last 24 months in 2010. Using the same rationale described for medical visits, these individuals were identified by an indicator variable for missingness and were included in the analyses for the year 2010, but not for 2000 and 2006. There was no association between missing information on preventative care in the last 24 months and the odds of polypharmacy in 2010. Individuals with missing values in 2000 (N=14, 0.65% of the 2000 sample) and 2006 (N=3, 0.21% of the 2006 sample) were not included in the regressions.

2.2 GEOGRAPHIC LEVEL DATA

2.2.1 Community Characteristics Calculated from the SABE Study Data

To allow for estimation of contextual effects (Aim 2) we calculated some community-level characteristics using aggregated information from SABE study participants (Table 2.3). The participant-derived community characteristics were obtained for each sub-prefecture. Each characteristic was calculated as a weighted average of the participants living in that area. Importantly, each characteristic reflects the average of the characteristic among older adults, and not the general population of the area.

Table 2.3 Community-level characteristics derived from the SABE Study

Variable	Definition
Drug Utilization	
Polypharmacy	% of individuals who were with polypharmacy
Socio-Demographic	
Age	Average age of the population in years
Gender	% of population who are females
Marital status	% of population who were married or in a civil union
Income	Average income in Brazilian Reais (R$)
Health Insurance	% of population with private health insurance
Health Status	
Chronic Diseases	Average number of chronic conditions per capita (conditions: hypertension, diabetes, heart disease, lung disease, stroke, cancer, psychiatric conditions, joint diseases, or osteoporosis)
Level of symptoms	Average number of clinical symptoms per capita (symptoms: persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo, tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence in the last 12 months)
Level of disability	Average level of disability per capita (activities: walking across a room, getting dressed, bathing, feeding, transferring to/from bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores)
Health Utilization	
Medical visits	Average number of medical visits in the last 12 moths per capita
Preventative exam	% of the population who underwent a preventative exam in the last 24 months (women: mammogram; men: prostate exam).
Behaviors	
Smoking	% of population currently smoking
Alcohol	% of population currently using alcohol

Note: Aggregated data from individuals 60 years old and over. Source: SABE database.

2.2.2 Characteristics Obtained from Official Government Sources

We obtained community characteristics (population composition, living conditions, health needs) and health systems characteristics (health resources and health utilization) for each sub-prefecture from publicly available government sources.

We collected sub-prefecture information corresponding to the same time periods for which we had individual-level information, i.e., years 2000, 2006 and 2010. When information from the same year was not available we collected the closest available year. Table 2.4 and Table 2.5 display the community and health systems

characteristics, respectively, at the sub-prefectures level. It is important to mention that, unless noted, these characteristics reflect the entire population of each subprefecture (not only the population of older adults).

Table 2.4 Community characteristics – Data availability and sources

Indicator	Year			Source
Reference Year	**2000**	**2006**	**2010**	
Population & Geography				
Area in 1,000km²	fixed			Municipalities Database, IBGE
Number of districts	fixed			Municipalities Database, IBGE
Total number of residents	2000		2010	Brazil Demographic Census
		2006		IBGE data, SEADE Foundation
% female residents	2000		2010	Brazil Demographic Census
		2006		Calculated from Census data
% residents over age 60	2000		2010	Brazil Demographic Census
		2006		Calculated from Census data
% non-white residents			2010	Brazil Demographic Census
Number of births	2003	2006	2010	Infocidade online database
% white newborns	2003	2006	2010	Infocidade online database
Avg. nr. years of Schooling[1]	2000			Brazil Demographic Census
% illiterate inhabitants	2000		2010	Brazil Demographic Census
Average per capita income[2]	2000		2010	Brazil Demographic Census
Households & Living Conditions				
Total nr. households	2000		2010	Brazil Demographic Census
Avg. persons per household	2000		2010	Brazil Demographic Census
% suboptimal households	2000		2010	Brazil Demographic Census
%households treated water	2000		2010	Brazil Demographic Census
% households treated sewage	2000		2010	Brazil Demographic Census
Avg. nr. rural areas[3]	2000		2010	Brazil Demographic Census
Any rural areas	2000		2010	Brazil Demographic Census
Nr. areas occupied by slums	2000	2008	2011	Infocidade online database
% allocated city tax	2005	2006	2010	Infocidade online database
Total sales, new apartments	2000	2006	2010	Infocidade online database
Illness Level				
All-cause mortality[4]	2000	2006	2010	Infocidade online database
External-Cause Mortality[5]	2000	2006	2010	Infocidade online database

Notes: [1]Heads of households only. [2]In Brazilian Reais. [3]Classification according to the census. [4]Available for seniors and for the general population. [5]Available for the general population. IBGE: Brazilian National Institute for Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística*), SEADE: Sao Paulo State Data Analysis Foundation (*Fundação Sistema Estadual de Análise de Dados*), Infocidade: information portal of the Urban Development Secretariat of the Sao Paulo Municipality (*Secretaria Municipal de Desenvolvimento Urbano*).

Table 2.5 Health systems characteristics – Data availability and sources

Indicator	Year				Source
Reference Year	**2000**	**2006**	**2010**	**2010**	
Health Professionals[1]					
Total nr. Physicians		2008	2010		CE info database
Nr. Generalists		2008	2010		CE info online database
Nr. Geriatricians		2008	2010		CE info online database
Nr. Other Specialists		2008	2010		CE info online database
Nr. Pharmacists		2006	2010		CE info online database
Nr. Family Health Teams		2006	2010		CE info online database
Health Facilities					
Pharmacies[1]				2015	Ministry of Health
Pharmacies[2]				2016	Apontador.com
Pharmacies, partners				2015	Ministry of Health
Primary care clinics[1]	2000	2006	2010		Infocidade online database
Urgent care clinics[1]				2013	SP Health Secretariat
Specialty clinics[1]				2013	SP Health Secretariat
Senior health clinics[1]				2013	SP Health Secretariat
Mental health clinics[1]				2013	SP Health Secretariat
Hospitals[3]	2000	2006	2010		CE info online database
Hospital beds[3]	2000	2006	2010		CE info online database
Primary care equipment[3]		2006	2010		CE info online database
Tertiary care equipment[3]		2006	2010		CE info online database
Health Services Utilization[1]					
Nr. enrolled in the FHP		2006	2010		CE info online database
Nr. elective hospitalizations	2003	2006	2010		CE info online database
Nr. urgent hospitalizations	2003	2006	2010		CE info online database
Total nr. hospitalizations	2003	2006	2010		CE info online database
Primary care visits			2010		SEADE online database
Specialized care visits			2010		SEADE online database
Urgent care visits			2010		SEADE online database
% full antenatal care		2007	2010		SEADE online database
% deliveries via c-section		2007	2010		SEADE online database

Notes: [1]Public health system only. [2]Private health System only. [3] Available for both public and private health systems. IBGE: Brazilian National Institute for Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística*), SEADE: Sao Paulo State Data Analysis Foundation (*Fundação Sistema Estadual de Análise de Dados*), Infocidade: information portal of the Urban Development Secretariat of the Sao Paulo Municipality (*Secretaria Municipal de Desenvolvimento Urbano*).

As can be seen from Table 2.4 and Table 2.5, some community and health systems characteristics were not available for the years corresponding to the SABE study. When a variable did not correspond to the specific years of the SABE study, we either avoided using it altogether (e.g., urgente and specialized health clinics), or used only its available years (e.g., availability of doctors); or used it in the sensitivity analyses (e.g., hospital admissions).

There were only two cases where we did data imputation for geographic-area variables. We interpolated the rural area indicator for 2006 assuming that areas with same rural/urban status in 2000 and 2010 were the same in 2006 (see Chapter 5). We could only obtain current information on number of private pharmacies per area. We calculated quintiles of greater concentrations of private pharmacies per area and we assumed that an area belonged to the same quintile over time (see Chapter 6).

3. CHAPTER III: PATTERNS OF DRUG UTILIZATION AND RISK AMONG OLDER ADULTS IN SAO PAULO, BRAZIL

ABSTRACT

Background: Pharmaceuticals can expose individuals to risks such as adverse effects and drug interactions. The possibility of risk tends to increase with each additional drug in a pharmaceutical regimen. Regimens of five or more drugs per day (polypharmacy) have been progressively frequent among older adults in Brazil. It is not clear whether all polypharmacy regimens are equally risky or what specific drugs or combinations of drugs are likely to cause greater risk in that population.

Aims: This study aimed to quantify the occurrence of inappropriate polypharmacy among the older adult population in Sao Paulo, characterizing its trends over time and its association with presence and type of drug risk. We focus on the risk from drug adverse effects, not the actual occurrence of events. We aim to capture the harm that could be averted if measures such as early detection and improved monitoring had been in place.

Methods: We used data from a household survey of older individuals age 60 years and older living in the community in the city of Sao Paulo, Brazil. We used three waves of this survey, collected in 2000, 2006, and 2010, to investigate time trends. We used the pooled sample, a total of 4,889 observations, to investigate the presence of adverse effects, using the Anticholinergic Risk Scale (ARS); clinically relevant drug-drug-interactions, using the Hines list; and inappropriate prescribing, using the Beers Criteria. Only prescription and over-the-counter drugs were examined.

Results: Drug risk was frequent, and strongly associated with higher number of drugs per day. About two-thirds of people with polypharmacy were exposed to some form of risk. There were no drug or drug combinations driving most of the risk. Levels of inappropriateness among people with polypharmacy tended to decrease over time, but drug interactions and anticholinergic potential tended to increase. The composition of drug treatments followed the patterns of the underlying health conditions reported by the participants.

Conclusions: The association between polypharmacy and drug risk should receive greater attention from public health decision-makers in Sao Paulo. Policies to reduce drug risk should target all older adults with polypharmacy. By introducing additional tools to capture additional dimensions of drug risk we empirically demonstrated the importance of a comprehensive drug risk assessment in population studies. Better tools that combine these and other dimensions of drug risk are necessary, especially to improve drug risk evaluations at the population level.

3.1 INTRODUCTION

3.1.1 Policy Problem: Assessing the Risk from Polypharmacy

There is evidence that the use of pharmaceuticals is very frequent among older adults in Brazil (Loyola Filho et al., 2005; Marin et al., 2008). There is also evidence that use of pharmaceuticals is growing, both in frequency and in number of drugs, among this population. Polypharmacy, the use of multiple drugs per day, is a special case of drug utilization that has increased sharply in recent decades (Loyola Filho et al., 2011).

The growing use of pharmaceuticals is a matter of public health concern. Even when prescribed correctly – for the right indication, at the right dose, and for the right duration – pharmaceuticals can expose individuals to unnecessary risk (Gomez et al., 2015). All drugs have potential adverse effects. Drugs may interact with each other increasing the risk of toxicity or treatment failure (Johnell & Klarin, 2007). The incorrect use of pharmaceuticals (such as non-adherence) may also increase the risk of complications (Simonson & Feinberg, 2005). Although it is not possible to predict which specific individuals will develop harmful effects from specific drugs or combinations of drugs, it is possible to identify drugs or combinations that pose greater risk, and populations that are most vulnerable.

The possibility of risk tends to increase with each additional drug in a pharmaceutical regimen. Regimens of five or more drugs per day have been associated with increased risk of frailty, falls, cognitive impairment, and mortality (Gnjidic et al., 2012). Therefore, a threshold of five or more drugs a day is generally used to define polypharmacy (Gnjidic et al., 2012).

Older adults are especially vulnerable the risk of adverse drug effects, especially the risk from polypharmacy. Older adults tend to have more comorbidities and lower metabolic capacity, which may increase their sensitivity to drug effects and drug risks. Yet, they tend to be prescribed more drugs more often than the rest of the population (Hovstadius, Hovstadius, et al., 2010).

Drugs are a modifiable exposure. Identifying situations of greater risk is important in order to adjust therapeutic regimens before they occur, avoiding reductions in quality of life; or increased risk of hospitalizations, or even deaths from drugs. Identifying precisely what causes the increased risk is challenging in the case of polypharmacy. It is not clear whether all polypharmacy regimens are equally risky or what specific drugs or combinations of drugs are likely to cause greater risk.

While clinicians may perform a case-by-case risk assessment for each patient with polypharmacy, policy makers face challenges regarding population-level decisions. Are all persons with polypharmacy a matter of concern? Or is the risk from polypharmacy mostly driven by specific drugs or drug classes that should themselves become the focus of attention?

We focus on drug adverse effect potential, or the "chance of causing harm", not the actual occurrence of harm (Edwards & Aronson, 2000). We aim to capture the harm that could be averted if measures such as early detection and improved monitoring had been in place.

Our ultimate goal is to inform public health decisions, primarily in the context of Sao Paulo. We aim to identify the magnitude of drug-related risks associated with polypharmacy among older adults and we aim to identify whether risk is most commonly related to polypharmacy in general or whether there are specific drugs and drug classes that are responsible for the increased the risk among that population.

Because drug-related risks depend on drug selection, all factors involved in drug selection provide potential targets for policies to reduce drug risk at the population level. In this context, prescription patterns and provider preferences matter; therapeutic guidelines matter; levels of health care integration across providers matter; drug formularies matter; and broader acceptability of drugs and awareness of drug risks by the general public also matter. However, determining which of these factors is not the objective of this chapter. The objective of this chapter is to determine how to measure inappropriate polypharmacy. Later chapters will examine the factors associated with greater levels of inappropriate polypharmacy.

If we find that polypharmacy is frequently associated with drug risk among Sao Paulo older adults, then it may be of policy-makers' interest to devise strategies to mitigate it. Not only older adults would be protected against

drug risks, but also there could be cost savings to the public health system with lower purchase of drugs and with lower expenditures from treating complications such as hospitalization.

If we find, for example, that most of the risk is associated with a specific drug or drug combination, then policies to reduce drug risk in older adults in Sao Paulo could focus on individuals exposed to those drugs and the reason why this is occurring. Policies could be put in place to identify individuals using these target drugs or drug combinations and provide them with safer alternatives, for example, or improve clinical monitoring. Or, drug formularies could be altered to promote safer drug choices and disincentivize the use of the problem drugs.

If, on the other hand, we find that drug inappropriateness is associated with cases of polypharmacy in general, then policies may be put in place to improve monitoring of polypharmacy among older adults in Sao Paulo.

3.1.2 Overview of Main Drug Risk Types

There are different classifications of drug risk (Davies, 1977). Most classifications focus on risks that are associated with the chemical properties of a drug and its pharmacologic effects on the body. This is the case of adverse effects and drug interactions, for example.

However, there are other forms of drug risk that arise not from the chemical properties of the drug itself, but from the process of treatment administration. The main examples are medication errors - when harmful clinical consequences arise from improper administration of a drug - and treatment burden - when there are losses of quality of life arising from the burden of maintaining multiple drug intakes a day.

In this study, we will focus on risks associated with drugs' chemical properties. While both medication errors and treatment burden can be associated with polypharmacy, their assessment relies heavily on clinical judgment and requires extensive information about the drug (dosage, frequency of administration) and the circumstances of treatment administration. These factors greatly limit the possibility of assessing treatment burden and medication errors from secondary data. The investigation of the relationship between polypharmacy and treatment burden and medication error in Brazil should be the focus of future studies. This is an important first step.

3.1.3 Adverse Effects

Adverse effects are probably the most commonly recognized type of drug risk. An adverse effect can be understood more broadly as any "adverse outcome that can be attributed to some action of a drug" (Edwards & Aronson, 2000). Adverse drug effects are a term interchangeable with adverse drug reactions. However, the term "adverse effects" is employed to reflect patients' perspective, while "adverse reactions" refers to the drug itself (Edwards & Aronson, 2000).

A more specific definition of adverse effect is an "appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (Edwards & Aronson, 2000).

Adverse effects can be classified according to their main underlying mechanism: dose-related (adverse effects that are triggered by higher doses of a drug, such as drug toxicity), non-dose related (idiosyncratic adverse effects), dose and time-related (chronic adverse effects), time-related (delayed or tardive adverse effects), withdrawal (adverse effects that are triggered by treatment discontinuation), and unexpected treatment failure (Davies, 1977).

The type, frequency, and severity of adverse effects are specific to each drug. There have been diverse attempts at developing classification systems of adverse effects. An example is the World Health Organization's Adverse Reaction Terminology (WHO Collaborating Centre for International Drug Monitoring). However, adverse effects classification systems are usually descriptive rather than predictive. These systems list the possible adverse effects associated with each drug. Their goal is to create a terminology that helps standardize reporting and recording of adverse effects (WHO Collaborating Centre for International Drug Monitoring) Adverse effect classification systems do not help predict which types of patients are more likely to develop a particular adverse effect, nor how severe an adverse effect would be in different clinical circumstances.

Tools that have been developed to predict the likelihood of adverse effects have focused on specific adverse effects or specific drug classes (Day, Wood, Dewey, & Bentall, 1995; Jung et al., 2005). However, there is not one single list of adverse effects that can be applied to examine all drugs being used by the general population. This is because what is an adverse effect in one case may be a desirable effect in another. For example, blood pressure-lowering effects may be the desired effect behind the prescription of anti-hypertensive. However, when a drug used to treat a different condition triggers hypotension, this may be undesired and harmful, representing an adverse effect.

In this study we focus our adverse effects investigation on anticholinergic adverse effects. Anticholinergic adverse effects are more frequent among older adults. Anticholinergic adverse effects occur when drugs interfere with the actions of the neurotransmitter acetylcholine. Acetylcholine is involved in numerous biochemical pathways in the body. In the peripheral nervous system acetylcholine is responsible for involuntary muscle movement, secretion of saliva, tears, and others. The main peripheral anticholinergic adverse effects are dry mouth, dry eyes, constipation, and urinary retention. In the central nervous system, acetylcholine is involved in many processes associated with attention, memory and balance. The main central anticholinergic adverse effects are dizziness, falls, confusion, and memory loss. We chose anticholinergic adverse effects because these effects can greatly impact quality of life and can be very severe (associated with physical and cognitive decline, for example) (Cancelli, Beltrame, Gigli, & Valente, 2009; Pasina et al., 2013).

A wide variety of drugs used to treat many different conditions can cause anticholinergic adverse effects. Therefore, the possibility of such effects is relevant to the entire population. Also, anticholinergic effects are rarely clinically desirable. This fact minimizes the possibility that a desirable effect might be misclassified as drug risk in our study.

3.1.4 Drug-Drug Interactions

Combinations of drugs can be riskier than each drugs taken in isolation. Drug-drug interactions (DDIs) occur when the effect of one drug is modified by the effect of another (Goldberg, Mabee, Chan, & Wong, 1996). DDIs may occur through pharmacokinetic changes (when a drug impacts the other's absorption, metabolism or

excretion) or through pharmacodynamic interactions (when there is synergism or antagonism between drug effects) (Mallet, Spinewine, & Huang, 2007).

DDIs are not necessarily negative. Some DDIs may be desirable if they result in enhanced beneficial effects from treatments – in cases of treatment synergy. Or, DDIs may not be clinically relevant – in some cases the effects of DDIs are negligible or not clinically noticeable.

DDIs become a matter of concern when they result in a significant reduction of the therapeutic effect of a drug or in a significant increase in the risk of adverse effects. In these cases, DDIs may have very severe clinical outcomes, leading to hospitalizations and even death. An example of clinically relevant DDI is the combination of an anticoagulant agent such as warfarin with a non-selective non-steroid anti-inflammatory agent (NSAID) such as diclofenac. The NSAID increases the likelihood of erosions in the gastro-esophageal mucosa, and the anti-coagulant prevents clot formation. When taken together, these drugs may result in major gastrointestinal bleeding, which can have disastrous consequences (Hines & Murphy, 2011).

In order to adequately assess the risk from DDIs it is important to have information on all drugs that are part of a therapeutic regimen, including prescription and over-the-counter drugs. The adequate detection of DDIs requires pairwise comparisons across all drugs in a regimen. It also requires a database where the evidence on drug combinations is regularly updated.

The best tools for the detection of DDIs are usually automated, computer-based systems. Hence, DDIs are most commonly and most comprehensively examined where detection systems are embedded in electronic prescribing platforms, such as in hospitals and other in-patient settings. The downside of automated DDI detection systems, however, is that they may be excessively sensitive and produce alerts for DDIs that are not clinically relevant. Over time, the overflow of non-relevant DDI alerts may de-sensitize prescribers reducing the usefulness of the information retrieved from these systems (Malone, 2007).

3.1.5 Inappropriate Prescribing

There are multiple dimensions to consider a treatment "appropriate". To be considered "appropriate", a drug should be prescribed in the right dose for the right indication, in a timely manner, be efficacious, safe, cost-effective, and respect patients' preferences (Hanlon & Schmader, 2013; Hanlon et al., 1992). For the purposes of drug risk assessment, appropriateness may be defined as a treatment which benefits exceed its risks (Shelton, Fritsch, & Scott, 2000).

Because of the increased vulnerabilities of older adults, many classifications of inappropriate prescribing have been developed specifically for that population. Inappropriateness may be an easier way to capture higher risk of adverse effects, as it specifies drugs that may pose greater risk for individuals based on their age or their underlying health conditions – in these circumstances, adverse effects have also been called "drug-age" or "drug-disease" interactions (Mallet et al., 2007).

Inappropriate prescribing encompasses several aspects of the fit between need and drug selection, from overprescribing (toxic doses or duplicate therapies) to under prescribing (not prescribing a needed therapy).

In this study we investigated the presence of three main drug risk categories: adverse effects, clinically relevant DDIs, and inappropriate prescribing. In order to measure each type of drug risk, we identified tools to assess drug risk from the medical literature. We discuss the tools in more detail below.

3.1.6 Tools to Assess Drug Risk

We screened our sample for adverse effects, potentially inappropriate prescribing, and potentially harmful drug-drug interaction. We selected among the tools developed specifically for the older adult population.

We selected tools that had been validated against significant clinical outcomes and that had been used in many references such as clinical studies or secondary data analysis. Although none of our selected tools had been developed specifically for the Brazilian context, most had been employed in other studies for similar objectives

(Davidoff et al., 2015; Lowry, Woodman, Soiza, & Mangoni, 2011; Pasina et al., 2013), including in Brazil (Baldoni Ade et al., 2014).

All the tools that we chose have been developed and published in a time frame that suits the period of the data collection for the SABE study. This is particularly important because prescription patterns change over time, as drugs may enter or exit the market, so that tools that have been developed too long before a study may not include drugs newly available at the time of the study. Conversely, tools developed long after the completion of a study may not include drugs that might have been widely used at the time of data collection but might have become obsolete at the time of the tool development.

3.1.7 Adverse Effects – Tool: Anticholinergic Risk Scale

We used the Anticholinergic Risk Scale (ARS) to detect the potential for anticholinergic adverse effects. The ARS scale was developed specifically for the geriatric population (Rudolph et al., 2008). The ARS assesses the potential for adverse effects from a given therapeutic regimen, and so it is an efficient tool to evaluate the risk to which patients are exposed even before any symptoms or signs have occurred.

The ARS has a list of frequently prescribed drugs and assigns a score to each drug according to their potential for anticholinergic adverse effects. Scores were defined by experts who reviewed chemical information (specifically, the dissociation constant for the cholinergic receptor (pKi), obtained from the National Institute of Mental Health psychoactive drug screening program), clinical information (rates of anticholinergic adverse effects when compared to placebo obtained from the Micromedex platform), and scientific evidence from peer-reviewed medical literature (reports of anticholinergic adverse effects catalogued in the Medline database of the National Library of Medicine). Each drug received a score varying from 0 to 3, were 0 represented no anticholinergic potential, 1 represented moderate, 2 represented strong, and 3 represented very strong anticholinergic potential. An example of a drug with a score of 0 is the antibiotic amoxicillin. An example of a drug with a score of 3 is the antipsychotic haloperidol. The total ARS score of a therapeutic regimen is calculated by the sum of individual scores of all drugs in the regimen.

The ARS has several limitations, for example it does not take drug dosage into consideration (which could further increase the likelihood of anticholinergic adverse effects for some drugs) and it does not include topical, ophthalmic, otologic, or inhaled medications (which could contribute, albeit little, to systemic anticholinergic activity if there was enough absorption of the drug through the mucosa). Also, it assigns similar scores to drugs that may have different degrees of anticholinergic activity (for example, a drug in category "3" can have higher anticholinergic potential than another one in the same category). The ARS sums the scores from each drug without consideration as to whether drugs may interact with each other. Lastly, there is variation between the ARS and other tools developed to identify anticholinergic adverse effects (Duran, Azermai, & Vander Stichele, 2013).

The ARS scale was validated in populations of older adults in primary care and hospital settings, both in the United States and abroad (Lowry et al., 2011; Pasina et al., 2013; Rudolph et al., 2008). Higher scores in the ARS scale were shown to be associated with an increased risk of central (dizziness, confusion, falls, and others) and peripheral (dry mouth, dry eyes, constipation, and others) anticholinergic adverse effects. Higher scores were also associated with lower cognition (as measured by the Short Blessed Test) and higher disability levels (as measured by the Barthel Index), even after adjustment for relevant factors such as age, education level, and neurologic conditions such as stroke or transient ischemic attacks (Lowry et al., 2011; Pasina et al., 2013). In one study, higher scores in the ARS scale were also associated with increases in mortality among patients experiencing hyponatremia, a frequent clinical complication in hospitalized settings (Lowry et al., 2011).

There are no defined cutoffs for the ARS scale. Total ARS scores as low as 1 or 2 points are statistically significantly associated with increased risk of anticholinergic adverse effects as compared to ARS scores equal to zero (Rudolph et al., 2008). Higher scores have been shown to be associated to greater risks of anticholinergic adverse effects in a dose-response relationship (Pasina et al., 2013). The distribution of ARS scores in the investigated populations tends to be right-skewed, with most scores in the lowest categories, including zero (Rudolph et al., 2008).

When compared to other scales developed to identify anticholinergic potential it has been suggested that the ARS scale may be more specific but less sensitive (Pasina et al., 2013). In other words, the scale does not explain all the occurrence of anticholinergic adverse effects in one population. Still, the ARS has been

demonstrated to correlate more efficiently than other scales with higher levels of clinically significant cognitive and physical impairment (Duran et al., 2013).

This scale has been validated for use in secondary data and for populations of older adults living in the community (Rudolph et al., 2008), like our sample. The ARS scale reflects a conservative estimate of the number of persons at risk of anticholinergic adverse effects. Because this scale is more specific than sensitive, it is likely that there will be persons at risk for anticholinergic adverse effects in our sample that will remain unidentified. However, when a person receives a non-zero ARS score, the likelihood that they are truly at risk of clinically relevant adverse effects is greater.

While tools to evaluate other types of adverse effects have been developed, they may be restricted to specific classes of drugs (Lingjaerde, Ahlfors, Bech, Dencker, & Elgen, 1987; Simpson & Angus, 1970), may require extensive information on the person's underlying health conditions and therapeutic characteristics to be implemented (Naranjo et al., 1981), or they may only be applicable once symptoms and signs of adverse effects are present (Morimoto, Gandhi, Seger, Hsieh, & Bates, 2004). Anticholinergic adverse effects may arise from a wide variety of drugs used to treat diverse conditions and organ systems, and the ARS accordingly covers a broad range of drug classes.

3.1.8 Inappropriate Prescribing – Tool: Beers Criteria

We used the American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults (Beers Criteria) to assess the possibility of inappropriate prescribing among our sample (AGS, 2012). The Beers Criteria is an explicit (criterion-based) tool to identify high-risk drugs that have an "unfavorable balance of risks and benefits" for the aging population (American Geriatrics Society Beers Criteria Update Expert, 2012).This is a very important tool to screen persons with polypharmacy because it helps identify which specific drugs may pose greater risk.

The Beers Criteria consist in a list of drugs that should be avoided in persons over age 65. The criteria are decided by expert consensus, based on evidence from systematic reviews and meta-analysis published in the

medical literature. The Beers Criteria divides drugs in two drug lists: drugs to be avoided in all older adults, and drugs to be avoided only if specific diseases or syndromes are present.

There are several advantages to employing a tool such as the Beers Criteria to screen individuals for increased risk of age-associated adverse effects in our sample. First, this list is very comprehensive. The Beers Criteria include from antibiotics to drugs used to treat common chronic diseases. Therefore, it is applicable to the general population of older adults in our study, who live in the community and who can be expected to have a wide variety of conditions. Second, the Beers Criteria describe drugs that should be avoided in all older adults regardless of underlying health conditions. This is also an advantage because we use secondary data and not all of the diagnoses of the participants may be known. Third, the Beers Criteria has been validated against hard clinical outcomes in many different populations, and it has been demonstrated to be valid and reliable to identify situations of greater drug risk that are associated with worse clinical outcomes (Kaufmann, Tremp, Hersberger, & Lampert, 2014; Koyama, Steinman, Ensrud, Hillier, & Yaffe, 2014). Lastly, the Beers Criteria are widely utilized in studies of older adults, facilitating comparison between the results of our study and results from other populations.

There are limitations to this tool; mainly, it does not take into consideration drug dosage, other treatments in use, and individual differences between patients, such as preferences and comorbidities. These aspects can be addressed by implicit (clinical judgment-based) tools applied on a case-by-case basis (Kaufmann et al., 2014). The Beers Criteria heavily focus the definition of inappropriateness on the potential for drug adverse effects. Other aspects of appropriateness, such as the potential for non-adherence, the cost-effectiveness profile of the drug, and the possibility of under-treatment, are left unaddressed. Also, the Beers Criteria do not recommend alternative, safer options to the drugs that they recommend should be avoided. Nevertheless, since their first development in 1991, the Beers Criteria have been widely used by clinicians and researchers, including for the analysis of secondary data.

In the present study we used the last update of the Beers Criteria, developed by the American Geriatrics Society in 2012, to identify potentially inappropriate prescribing in our sample. Due to data limitations we used only the component of the Beers Criteria applicable to all older adults irrespective of underlying diagnoses. Out of the 150-plus drugs in this component we were not able to examine four drugs whose analysis required dosage

information (reserpine, aspirin, digoxin and spironolactone). We examined the sliding-scale insulin criteria using fast-acting human insulin (ATC code A10AB01) as a proxy.

3.1.9 Drug-Drug Interactions – Tool: Hines' Review of Potentially Harmful Drug-Drug Interactions in the Elderly

In order to examine the presence of DDIs in our sample, we used a list of potentially harmful DDIs compiled by Hines and Murphy from a reviewed of evidence from the medical literature focusing specifically on the population aged 65 and over (Hines & Murphy, 2011). The final list comprehends over 20 drug classes in pairwise combinations. All listed DDIs are severe and clinically relevant, as they are associated with significantly increased risk of hospitalization or mortality among the elderly.

We opted for applying the Hine's list to identify DDIs in our sample because of its direct relationship with clinically relevant outcomes. Although the list itself has not been validated as a tool, each of the interactions that it contains has being explicitly validated against hard clinical outcomes such as hospitalization or mortality. Because our main goal was to identify high-risk types of polypharmacy we wanted to minimize the possibility of false-positives that could arise from using a computerized DDI screening tool. The results from a previous study investigating the possibility of DDIs in the first wave of the SABE survey corroborate our rationale (Secoli, Figueras, Lebrao, de Lima, & Santos, 2010). This study, which used a commercial computerized system (Micromedex ®) to identify DDIs, found a very high number of individuals exposed to a potential DDI (over 50% of individuals who took two or more drugs). However, the vast majority (80%) of the DDIs identified were of mild to moderate severity. The most frequently identified DDI combinations in that study were captured in the Hines DDI list, indicating that the Hines list may be an appropriate tool to screen for relevant DDIs in our sample.

3.2 AIMS

The overall aim of this study is to quantify the occurrence of drug adverse effect potential among the older adult population in Sao Paulo, characterizing the type and level of risk, and its association with polypharmacy.

Specifically, we aim to: 1) measure the overall prevalence of polypharmacy among older adults in Sao Paulo; 2) quantify the occurrence of drug risk among those with polypharmacy, assessing the types and levels of risk; 3) identify time trends in the occurrence of polypharmacy and in its association with drug risk among this population; and 4) identify which drugs are most frequently associated with risk.

3.3 METHODS

3.3.1 Data

Overview of the SABE Study

We use data from a household survey of older individuals age 60 years and older living in the community in the city of Sao Paulo, Brazil – the SABE study (*Saúde, Bem-Estar e Envelhecimento* – Health, Wellbeing and Aging). This survey was modeled on the United States Health and Retirement Study. The survey was carried out by the University of Sao Paulo in partnership with the Pan-American Organization in 2000, and replicated by the team of investigators from University of Sao Paulo in 2006 and 2010.

The SABE study aimed to assess overall patterns of health and wellbeing among the Sao Paulo older adult population. The survey employed a multi-stage sampling process based on the Sao Paulo census frame. Individuals aged 75 and older were oversampled. When weighted by the inverse probability of selection the SABE sample is representative of the non-institutionalized population of 60 year-olds and over living in Sao Paulo in each of the survey years. The study's sampling process and data collection protocols were described in more detail earlier and in scientific publications (Lebrao & Duarte, 2003; A. Palloni, Pinto-Aguirre, & Pelaez, 2002).

3.3.2 Variables

The SABE study collected extensive personal and clinical information, mostly through self-report. When individuals were unable to adequately inform, interviews were conducted with a proxy. A summary of the main variables collected in the SABE study is presented in Chapter 2.

Demographic characteristics collected included age, gender, marital status (binary coded as married or in a civil union versus single, widowed or divorced), race (binary coded as white versus other), and religion (binary coded as catholic versus other). Socio-economic characteristics included years of schooling (number of school years completed; repeated grades were not considered), number of people who lived in the household, having living children (yes, no), having a caregiver (yes, no), and per capita income. Income was measured in Brazilian Reais. Participants were asked to inform their total income per month from all different sources (wages, investments, pensions, rent, remittances, etc.). Per capita monthly income was calculated by dividing the total reported income by the number of people that depended on the income as informed by the participants.

Health care utilization characteristics included health insurance coverage status (having or not having private health insurance), number of physician visits in the last 12 months, and whether the participant underwent a preventative exam (mammogram for women and prostate exam for men) in the last 24 months.

Health status characteristics included presence and type of chronic conditions, presence and type of symptoms, level of disability, and self-reported health status.

Information on chronic disease was obtained by asking participants if they were ever diagnosed by a doctor or nurse with one or more of the following conditions: hypertension, diabetes, heart disease, lung disease, stroke, neuropsychiatric disorders, cancer, osteoporosis, and arthritis. Positive responses were aggregated to obtain the number of chronic diseases reported by each participant.

Information on symptoms was obtained by asking participants whether they experienced any of the following symptoms in the last 12 months: persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo,

tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence. Positive responses were aggregated to obtain the number of symptoms reported by each participant.

Information on disability was obtained by asking participants whether they had difficulties performing one or more activities of daily living: walking across a room, getting dressed, bathing, feeding, transferring to/from bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores. Positive responses were aggregated to obtain the level of disability reported by each participant.

Self-reported health status was obtained by asking participants how they assessed their current health. Participants could choose from the following options: excellent, very good, good, regular, bad, or very bad health. The information provided by the participants was aggregated to create a binary variable "good" (excellent, very good, or good) versus "bad" (regular, bad or very bad) health status.

Health behavior characteristics included smoking, alcohol, and self-medication habits. Smoking was classified as currently smoking versus not currently smoking. Alcohol use was classified as current alcohol use versus no current alcohol use. Self-medication information was obtained by asking who had issued the prescription for each of the drugs that a participant was using. If any of the drugs been started by the participant on their own will or on recommendation from family members/ friends, without a prescription issued by a health provider, the information was recorded as self-medication. If all drugs were prescribed by a health professional, or if the person did not take any drugs, the information was recorded as no self-medication.

3.3.3 Drug Utilization

Although medicines were not the primary focus of the SABE survey, comprehensive information on drug utilization was collected from both participants' self-report and from investigators' direct observation of pill bottles, blister packs, and medicine boxes. Information on drug dosage or number of intakes a day was not collected. All types of pharmaceutical products were recorded. That included prescription and over-the-counter drugs, compounded drugs, and herbal and homeopathic products.

The SABE study recorded prescription and over-the-counter drugs using the World Health Organization's Anatomical Therapeutic Chemical (WHO-ATC) classification. The goal of the WHO-ATC classification is to operationalize drug utilization research, providing a "standard language" for "exchanging and comparing data on drug use at international, national or local levels" (WHO Collaborating Centre for Drug Statistics Methodology).

The WHO-ATC classification indexes active ingredients of allopathic drugs using alphanumeric codes. In this classification the drugs are first divided according to the organ or system in which they act (level 1), and then they are progressively subdivided according to therapeutic subgroup (level 2), pharmacological subgroup (level 3), and chemical subgroup (level 4). The final level (level 5) identifies the specific drug (WHO, 2017). The WHO-ATC classification does not include products such as herbal and homeopathic preparations.

As an example, we present the WHO-ATC code for the commonly used painkiller acetaminophen, also called paracetamol and commercially available as Tylenol®. The main WHO-ATC code for paracetamol is N02BE01. The code reveals the following information (Box 3.1):

Box 3.1 WHO-ATC code for paracetamol

N Nervous System N02 Analgesics N02B Other Analgesics and Antipyretics N02BE Anilides N02BE01 paracetamol

Source: WHO-ATC index, https://www.whocc.no/atc_ddd_index/?code=N02BE01

There are 14 therapeutic groups represented as first-level categories in the WHO-ATC classification (Box 3.2):

Box 3.2 WHO-ATC therapeutic groups

Code	Contents
A	Alimentary tract and metabolism
B	Blood and blood forming organs
C	Cardiovascular system
D	Dermatologicals
G	Genito-urinary system and sex hormones
H	Systemic hormonal preparations, excluding sex hormones and insulins
J	Anti-infectives for systemic use
L	Antineoplastic and immunomodulating agents
M	Musculo-skeletal system
N	Nervous system
P	Anti-parasitic products, insecticides and repellents
R	Respiratory system
S	Sensory organs
V	Various

Source: WHO-ATC index, https://www.whocc.no/atc_ddd_index/

Each of the allopathic drugs in use by a SABE participant was recorded not by the drug's name, but by the drug's alphanumeric WHO-ATC code. General labels specifying their category recorded herbal, homeopathic, and compounded products. The labels did not contain information on the product's active ingredients, preventing us from using herbal, homeopathic, and compounded products in our analysis.

Using the survey information we created an indicator variable to identify polypharmacy (individuals using five or more prescription or over-the-counter drugs) and an indicator variable to identify excessive polypharmacy (individuals taking ten or more prescription or over-the-counter drugs).

We also counted the number of different WHO-ATC level-1 categories that were represented in each participant’s drug regimen. A larger number of WHO-ATC categories reflected persons taking drugs to treat multiple organs or systems. If a person was taking five drugs to treat asthma, for example, their number of medicines in use would be five, they would classify as polypharmacy, but they would have only one WHO-ATC category.

A participant recorded drug expenditures as the total amount reportedly spent on pharmaceuticals, in Brazilian Reais, in the last month.

3.3.4 Implementation of the Drug Risk Assessment Tools

The prescription and over-the-counter drugs used by the SABE study participants had been recorded using WHO-ATC codes. In order to operationalize the analysis of participants' drug regimens, we encoded the drugs listed in our selected tools using the same WHO-ATC classification.

Each of the tools that we selected contained a list of drugs that were associated with a particular type of risk. We converted the drug names provided in each of the tools into the drugs' corresponding WHO-ATC codes. We defined two guidelines when encoding the drug names. First, all the tools focused on drugs of oral use. Therefore, in the case that the WHO-ATC classification provided more than one code for the same drug according to the mode of utilization (oral versus topic), we applied only the code that corresponded to the drug's oral preparation.

Second, the WHO-ATC classification provides different codes for the same drug according to whether the drug is part of a single or combined preparation. For example, the acetaminophen in Tylenol is coded as N02BE01 because it is the only active ingredient in the pill. The acetaminophen in Excedrin, however, is coded as N02BE51 because the pill is a combination of acetaminophen and caffeine. We were interested in capturing all the possible commercial preparations of each drug; therefore, we applied all single- and combined-preparation codes for each drug provided in the WHO-ATC classification, as long as they corresponded to oral use.

We systematically evaluated the drug regimens from each of the SABE participants using our selected drug risk tools. We used Stata Statistical Software[9] to automate the application of the tools to the SABE dataset. The software compared the WHO-ATC drug codes in each participant's record to the WHO-ATC drug codes listed in each of the tools.

For the Beers Criteria, the software produced a binary result for each drug that the participant was taking. If there was no match, i.e., if the drug was not part of the Beers Criteria, the result was zero. If there was a match, i.e., if the participant's drug was part of the Beers Criteria, the result was one.

[9] Stata Statistical Software: Release 12. StataCorp. 2011. College Station, TX: StataCorp LP.

The results from the Beers Criteria were used to create two variables: one variable indicated the presence of any inappropriateness. This variable was equal to one if any of the participant's drugs matched the Beers Criteria. The other variable indicated the total level of inappropriateness identified in the participant's drug regimen. This variable was equal to the total number of drugs in a participant's regimen that matched the Beers Criteria.

For the ARS scale, the software produced a categorical result attributing a score to each of the drugs. Again, if there was no match between the participant's drug and the ARS scale, the result was zero. When there was a match between the participant's drug and the ARS scale, the result corresponded to the drugs' score in the ARS. For drugs identified in the ARS as having no anticholinergic potential the result was zero; for drugs with moderate anticholinergic potential the result was one; for drugs with strong anticholinergic potential the result was two; and for drugs with very strong anticholinergic potential the result was three.

The results from the ARS scale were used to create two variables: one variable indicated the presence of any anticholinergic drug risk. This variable was equal to one if any of the participant's drugs had a score equal to or greater than one in the ARS scale. The other variable indicated the total anticholinergic risk represented in the participant's drug regimen. This variable was equal to the sum of ARS scores for all the drugs that a participant was taking.

For the Hines DDI list, the software analyzed not drugs, but drug combinations. The software first identified whether each drug in a participant's regimen was part of the Hines list. If yes, the software then analyzed all the other drugs in the regimen to check if they presented a DDI combination with the first drug. The software produced two variables for each participant. The first variable indicated the presence of any DDI combinations in a participant's regimen. The second variable indicated the total number of DDI combinations in a participant's regimen.

3.3.5 Analysis

In the first part of the analysis we examined the combined pool of all participants in the SABE study. This analysis reflects average patterns across the three survey waves. We did not employ inverse-probability weights in the pooled analysis. Its intent was descriptive; no inferences regarding the overall population were made.

The pooled analysis examined overall sample characteristics as well as general patterns of drug utilization and drug risk. Specifically, we examined the main characteristics of SABE participants, the overall frequency and level of drug use; the distribution of drug risk criteria across the overall sample and across different levels of drug utilization; the relationship between the multiple risk measurements; and the relationship between drug risk levels and clinical characteristics.

In the second part of the analysis, we examined the sample from each of the survey waves separately. We applied the survey's inverse-selection probability weights to reconstruct the Sao Paulo population of older adults in each of the survey years. This analysis reflects year-specific estimates of patterns of drug utilization and drug risk among the Sao Paulo older adult population.

The cross-sectional analysis examined differences over time in drug utilization and drug risk. We examined drug utilization trends by therapeutic drug class; trends in prevalence and levels of chronic diseases; and trends in utilization of drugs according to the ARS scale and the Beers Criteria.

We utilized cross-tabulations and graphs to explore the associations between polypharmacy and inappropriate polypharmacy. We used Chi-squared tests (in the case of dichotomous or categorical variables) and t-tests (in the case of continuous variables) to compare characteristics across persons with and without polypharmacy or drug inappropriateness. We used Stata Statistical Software to perform most of the analysis, and Microsoft Excel[10] to produce some of the graphs.

[10] Microsoft. Microsoft Excel. Redmond, Washington: Microsoft, 2003.

3.4 RESULTS

3.4.1 Part I – Pooled Analysis

Sample Characteristics - Overview

The final sample of the SABE study constituted of a total of 4,889 participants distributed as follows: 2,143 participants in 2000, 1,413 participants in 2006 and 1,333 participants in 2010. Out of the total 4,889 participations in the SABE study 2,796 (57%) individuals participated in only one wave; 1,408 (29%) participated in two waves; and 685 (14%) participated in the three survey waves[11].

The main characteristics of the SABE study participants - demographic, socio-economic, health status, health care utilization and health behavior - are displayed in Table 3.1.

In summary, participants in the pooled SABE sample tended to be women on their mid-70's, who were white, catholic, and married, tended to have low- to medium socioeconomic status, to be in poor health, to have about two comorbid chronic conditions and to have disability about two activities of daily living. Participants frequently utilized health services but most often were not covered by private health insurance. Unhealthy behaviors such as smoking, drinking, and self-medicating were infrequent. We describe and discuss each of the characteristics in more detail below.

[11] There may be correlations across participants in each of the survey waves, as some individuals participated multiple times. We do not believe this was a major limitation, because most individuals participated in one single wave and those who participated in more than one were distributed across the three years.

Table 3.1 Characteristics of the SABE study participants (pooled sample)

Variable	N	Mean (sd)
Demographic		
Age	4889	73.39 (9.03)
Female gender	4889	0.61 (0.49)
Married	4889	0.51 (0.51)
White race	4889	0.67 (0.48)
Catholic religion	4889	0.69 (0.53)
Socio-Economic		
Years of education	4872	4.11 (3.92)
Per capita income (R$)	4258	580.76 (1002.1)
Nr. people in household	4886	2.95 (1.67)
Nr. of alive children	4761	3.47 (2.47)
Has caregiver	4889	0.27 (0.44)
Health Status		
Good self-reported health	4821	0.45 (0.48)
Any chronic diseases	4889	0.83 (0.37)
Nr. chronic diseases	4889	1.97 (1.46)
Nr. of symptoms	4887	1.53 (1.63)
Nr. ADLs with disability	4888	1.93 (2.96)
Health Care Utilization		
Health insurance	4886	0.43 (0.49)
Medical visits last 12 months	4483	6.02 (10.28)
Preventative exam last 24 mo.	4609	0.58 (0.60)
Health Behaviors		
Currently smoking	4887	0.12 (0.33)
Current alcohol use	4884	0.28 (0.45)
Self-medication	4887	0.28 (0.45)

Notes: N: number of participants with information. ADL: Activities of daily living.

The SABE study participants were on average 73 ± 9 years old. The minimum age was 60 years and the maximum age was 104 years. Most of the participants (61%) were female, married (51%), white (67%) and catholic (67%).

Participants completed on average 4.1 years of education. The minimum was no formal education (zero years) and the maximum was 22 years of education. The average monthly per capita income was R$ 580.76. This

amount represented almost 2 times the minimum wage.[12] The median income was R$ 340.00, which was about the minimum wage. Income varied from no income (if an individual had no personal income and depended exclusively on others) to a maximum of R$ 25,000.00 per month. The relatively high average income observed in the sample was driven by a very right-skewed distribution that likely reflects the very stark income inequality in the city of Sao Paulo. Most participants (96%) had at least one child who was alive. On average participants had 3.5 living children. Twenty-seven percent of participants had a caregiver.

Less than half of participants (45%, n=2161) reported feeling in good, very good, or excellent health. Most participants (55%, n=2660) felt in regular, bad, or very bad health. The information on chronic diseases, symptoms and disability levels is in line with this finding. Less than a fifth of participants (17%, n=806) did not have a chronic disease; 83% had at least one chronic disease. Each individual had, on average, about 2 chronic diseases. The maximum number of chronic diseases was eight, which is very high given that information was collected on only nine chronic conditions. The most common number of chronic conditions was two per person (26% of participants, n=1285, and only about 6% of participants than five or more chronic diseases.

The level of clinical symptoms and the level of disability reflect the severity of disease. These characteristics are important to differentiate between individuals with chronic conditions that are stable and under control from individuals who have a greater burden from the chronic conditions. The number of symptoms captures the degree to which a participant feels clinically unwell. The level of disability captures the degree to which the participant is impaired in their capacity to perform activities of daily living.

Participants reported an average of 1.5 symptoms. The minimum number of symptoms per person was zero (no symptoms) and the maximum was eight. Most individuals (34%, n=1683) had no symptoms. About 7% of participants had five or more symptoms. Three participants (0.06%) reported experiencing all of the eight symptoms investigated.

[12] The minimum wage mid-period between 2000 and 2010 was R$ 300. The minimum wave in Brazil was R$ 180.00 in 2000 and reached R$ 510.00 in 2010. Numbers are not adjusted for inflation; therefore, they reflect actual values in each year. Source: http://www.contabeis.com.br/tabelas/salario-minimo/

Participants reported disability in performing an average of 1.9 activities of daily living. The majority of participants (51%, n=2501) did not have any disability. Fourteen percent (n=692) of participants reported disability in performing one activity of daily living; 18% (n=892) had disability in two, three or four activities; and about 16% (n=804) had disability in five or more activities of daily living. Of note, 99 participants (2%) reported disability in all 12 activities of daily living investigated in the survey.

Less than half of participants had private health insurance (43%, n=2084). The majority of participants (57%, n=2802) depended exclusively on the public health system to obtain their care. Yet, participants reported an average of six medical visits in the last year, and the majority of participants reported having undergone a preventative exam in the last two years.

Twelve percent of participants reported currently smoking (n=589); 28% reported currently using alcohol (n=1373) and 28% reported self-medicating (n=1837).

Drug Utilization in the Pooled Sample

The majority of SABE participants took at least one prescription or over-the-counter drug. In summary, participants tended to use multiple drugs belonging to diverse therapeutic groups. Polypharmacy was relatively common but excessive polypharmacy was rare. Use of herbal and homeopathic products was relatively frequent, but participants tended to use very low numbers of these products as compared to prescription or over-the-counter drugs. Out of pocket drug expenditures were in general low. We describe the main drug utilization characteristics of the SABE study participants in greater detail below (Table 3.2).

Table 3.2 Overview of drug utilization metrics among SABE participants

Variable	N	Mean (sd)
Drug Utilization		
Taking at least one drug	4889	0.86 (0.35)
Nr. medicines in use	4889	3.25 (2.59)
Nr. WHO-ATC categories	4889	2.15 (1.48)
Polypharmacy	4889	0.27 (0.44)
Excessive polypharmacy	4889	0.02 (0.16)
Any herbal/homeopathic drug	4889	0.31 (0.46)
Nr. herbal/homeopathic drugs	4889	0.43 (0.79)
Drug expenditure (R$)	4317	64.87 (112.93)

Note: WHO-ATC: World Health Organization's Anatomical Therapeutic Chemical classification; Drug Expenditure: self-reported out-of-pocket payments with drugs on the last month, in Brazilian Reais.

Most participants (86%, n=4196) were taking at least one prescription or over-the-counter drug at the time of the survey. Fourteen percent (n=693) were not taking any prescription or over-the-counter drug. Participants used on average 3.25 prescription or over-the-counter drugs, corresponding on average to 2.15 therapeutic groups of the WHO-ATC classification.

About 27% of participants were with polypharmacy (n=3562); about 2.5% (n=121) were on excessive polypharmacy. The maximum number of prescription or over-the-counter drugs reported by a participant was 17 drugs. About 30% of participants (n=1501) took at least one herbal or homeopathic product. On average, participants took less than one herbal or homeopathic product. When all types of pharmaceutical products were considered, the maximum number of pharmaceutical products reported by a participant was 19.

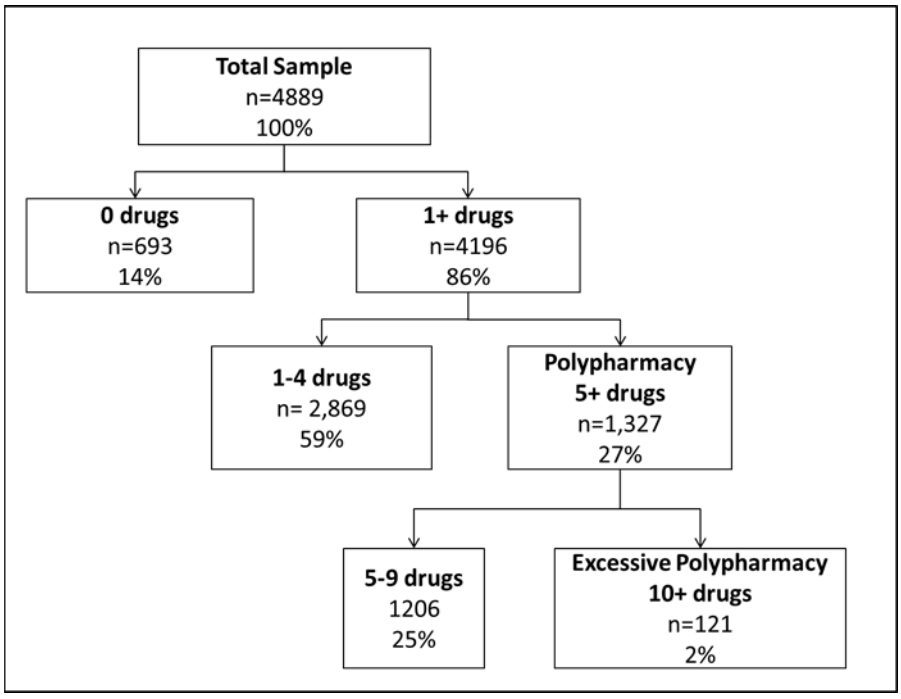
Information on drug expenditures was missing for 12% of participants (n=572). Those with information reported spending an average of R$ 64.87 per month on pharmaceuticals. The median monthly expenditure with pharmaceuticals was R$ 25.00. Participants reported spending up to R$ 2,000.00 per month on pharmaceuticals.

About 20% of individuals with spending information (870 out of 4317 participants) reported not having spent money on pharmaceuticals in the last month. Of those who were taking drugs 19.5% also reported not having spent any money on pharmaceuticals in the last month (829 out of 4244 individuals).

Figure 3.1 displays the overall pattern of drug utilization among the participants. The overall distribution of drug utilization in the pooled SABE sample was as follows: from the total 4,889 participants, 693 (14%) were not taking any drugs and 4,196 (86%) were taking at least one prescription or over-the-counter drug.

A total of 2,869 participants (59% of the sample, 68% of those taking drugs) were using drugs but not polypharmacy (1-4 drugs). A total of 1,327 individuals (27% of the sample, 32% of those taking any drugs) were with polypharmacy (5 or more drugs). Of those, 121 individuals (2% of the total sample) were taking excessive polypharmacy (10 or more drugs).

Figure 3.1 Pattern of drug utilization among pooled SABE participants



Note: Only prescription and over-the-counter drugs are included in the analysis.

Inappropriate polypharmacy - Patterns of drug risk in the pooled sample

Overall, 2012 (41%) of the individuals in our sample had at least one criterion for increased drug risk. The possibility of drug risk was higher among participants with polypharmacy (66%) and on those with excessive polypharmacy (84%) than among those taking drugs but not with polypharmacy (31%) (Table 3.3).

The Beers Criteria was most common form of drug risk identified in our sample. Anticholinergic effects measured by the ARS scale and DDIs measured by the Hines' List were the second and third most frequent forms of drug risk. Of the overall sample, 38% of participants had at least one drug that was part of the Beers Criteria, 13% had at least one drug that had anticholinergic properties, and 2% had a clinically relevant drug interaction (Table 3.3). The average Beers score across the pooled sample was 0.49. The Beers score reflects the total number of drugs from a person's pharmaceutical regimen that are identified as potentially inappropriate by the Beers Criteria. This indicates that the average person tended to be taking half a Beers-criteria drug. Of the 1,835 participants who had a positive Beers criterion, 74% (n=1,364) had only one drug that was potentially inappropriate; 21% (n=382) had two drugs, 4% (n=73) had three drugs and 1% (n=16) had four drugs that were potentially inappropriate.

The average ARS score across the pooled sample was 0.32. Differently from the Beers, the ARS score is not a simple count. Rather, the ARS score reflects the total anticholinergic potential of a person's pharmaceutical regimen. Each separate drug contributes points to the total score according to its anticholinergic potential: a drug can have from 0 points - no anticholinergic potential - up to 3 points – very strong anticholinergic potential. A person's total ARS score is the sum of all points corresponding to the drugs in their pharmaceutical regimen.

Out of 619 individuals who had a positive ARS score, 48% (n=298) had a total ARS score of 3. These individuals could be taking one single drug with very strong anticholinergic potential (3 points), or they could be taking combinations of drugs with moderate (1 point) or strong (2 points) anticholinergic potential. The next most common ARS score was 1 (n=165, 27%), indicating individuals who were taking only one drug with moderate anticholinergic potential (1 point). ARS scores higher than 3 were rare (less than 10% of those with positive ARS score). However, ARS scores were as high as 12. This score could reflect drug combinations of, for example, four drugs with very strong anticholinergic potential (3 points each), or six drugs with strong anticholinergic potential (2 points each), etc.

Drug interactions were very rare in our sample. Only about 2% of the participants (n=88) had a drug interaction captured by the Hines list. Most of them had only one DDI; three people had two DDIs and one had three DDIs. We describe the relationships between drug risk and number of drugs in the next section.

Table 3.3 Patters of drug risk in the pooled sample and according to the number of drugs

Variable Mean (sd)	All sample N=4889	1-4 drugs N=2869	5-9 drugs N=1206	10+ drugs N=121	p-value
Any risk criteria	0.41 (0.49)	0.39 (0.49)	0.66 (0.48)	0.84 (0.37)	<0.0001
1 Criteria	0.31 (0.46)	0.32 (0.47)	0.46 (0.50)	0.33 (0.47)	<0.0001
2 Criteria	0.10 (0.30)	0.07 (0.26)	0.19 (0.39)	0.49 (0.50)	<0.0001
3 Criteria	0.00 (0.05)	0.00 (0.00)	0.01 (0.09)	0.02 (0.16)	<0.0001
Any BEERS Criteria	0.38 (0.48)	0.36 (0.48)	0.58 (0.49)	0.81 (0.39)	<0.0001
BEERS score	0.49 (0.73)	0.42 (0.61)	0.85 (0.91)	1.41 (0.96)	<0.0001
Any ARS drug	0.13 (0.33)	0.10 (0.30)	0.23 (0.42)	0.48 (0.50)	<0.0001
ARS score	0.32 (0.94)	0.24 (0.77)	0.58 (1.24)	1.38 (2.03)	<0.0001
Any DDI	0.02 (0.13)	0.00 (0.05)	0.05 (0.22)	0.09 (0.29)	<0.0001

Notes: ARS: anticholinergic risk scale; DDI: drug-drug interaction. p-values correspond to the comparison across the three drug utilization groups (1-4 drugs, 5-9 drugs, and 10 or more drugs) and were calculated by F-tests in linear regressions of each risk variable on the three drug groups. The sum of the two columns – 5-9 drugs and 10+ drugs – represents the group of individuals with polypharmacy.

Relationship between number of drugs and presence and type of drug risk

All measures of drug risk tended to increase at greater numbers of drugs in a pharmaceutical regimen (Table 3). Any drug risk was present in 39% of persons taking 1-4 drugs, 66% of those taking 5-9 drugs, and 84% of those taking 10 or more drugs (Figure 3.2).

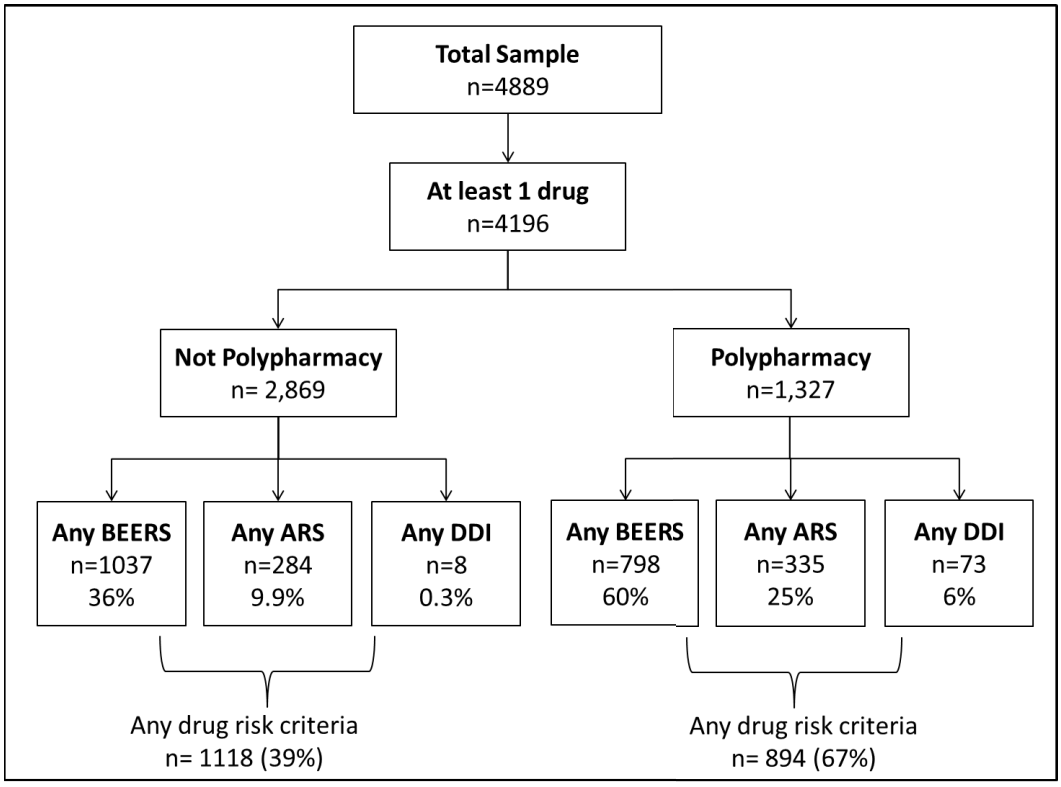
In univariate analyses, persons with polypharmacy had about three times greater odds of any drug risk as compared to persons taking drugs but not polypharmacy (odds ratio: 2.97; 95% confidence interval: 2.62 – 3.38). Persons on excessive polypharmacy had over eight times greater odds of any drug risk as compared to those taking 1-4 drugs (odds ratio: 8.41, 95% CI: 5.12 – 13.80). Each additional drug on a therapeutic regimen increased the odds of drug risk by about 50% on average (odds ratio: 1.52, 95% CI: 1.48 – 1.57).

The main form of drug risk identified in all utilization groups was captured by the Beers Criteria: 36% of those taking 1-4 drugs, 58% of those taking 5-9 drugs, and 81% of those taking 10 or more drugs had at least one potentially inappropriate drug identified by the Beers Criteria. Beers scores also tended to increase as the number of drugs in a pharmaceutical regimen increased – the average Beers score in the 10+ drugs group was over three times higher than the average score of those taking 1-4 drugs. Each additional drug increased the odds of having positive Beers Criteria by about 40% on average (odds ratio: 1.43, 95% CI: 1.39 – 1.47).

A similar pattern was observed in the distribution of anticholinergic risk as measured by the ARS scale. Any anticholinergic risk was over two times more frequent among persons taking 5-9 drugs (23%) and over four times as frequent among those taking 10 or more drugs (48%) than among persons taking 1-4 drugs per day (10%).

The distribution of DDI was markedly associated with increased number of drugs in a therapeutic regimen- of the 81 persons with a DDI, about 76% (n=62) were taking 5-9 drugs and 14% (n=11) were taking 10 or more drugs. It is important to mention, however, that about 10% of DDIs occurred among persons taking 1-4 drugs. Also, the highest number of DDIs – 3 DDIs – was identified in a participant taking four drugs (Glibenclamide, Nifedipine, Erythromycin and Buspirone). Figure 3.2 displays the overall pattern of drug risk identified in the pooled SABE sample. Only participants who took at least one drug are displayed.

Figure 3.2 Patterns of drug risk among participants with and without polypharmacy



Relationship between the different drug risk metrics

As shown in Figure 3.2, 67% of persons with polypharmacy had at least one drug risk criterion, as opposed to 39% of those without polypharmacy. In general (unadjusted analyses), polypharmacy was associated with a 70% greater probability of having at least one drug risk criterion in our sample.

Figure 3.2 also shows that there was an overlap between some of the criteria – people scoring on two or more criteria. Among those without polypharmacy, a total of 1329 different risk criteria were identified, but only 1118 participants had a positive criterion. In this group, 211 individuals had some overlap between the metrics. Among those with polypharmacy, the overlap was even higher. A total of 1206 different criteria were identified, but only 894 persons had a positive drug risk criteria. In this group, 312 individuals had some overlap between the metrics.

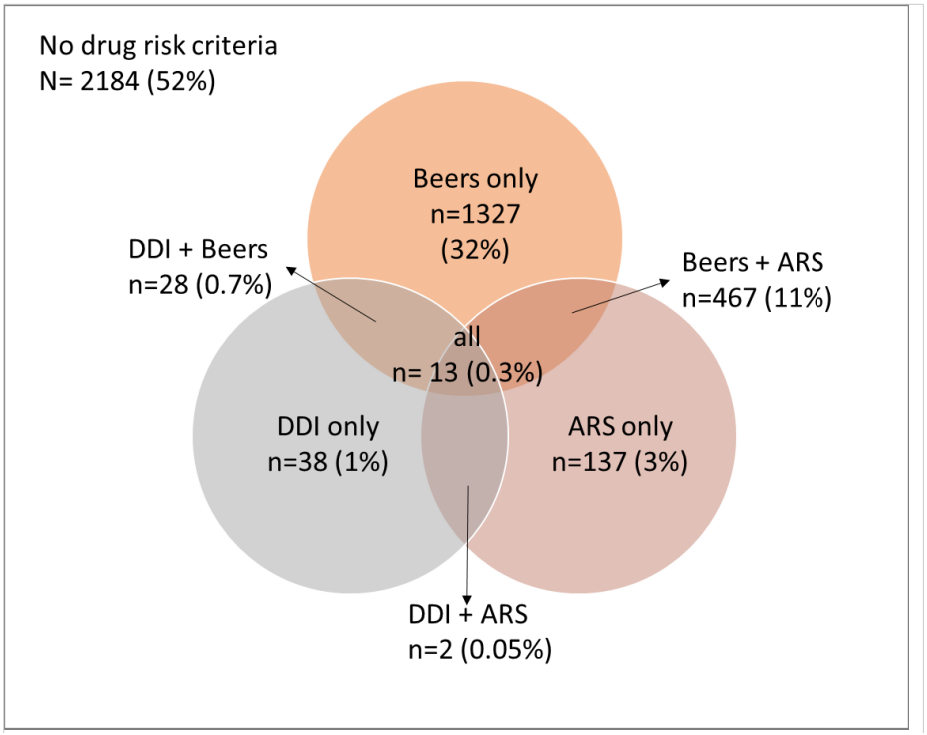
We explore the degree of overlap between the metrics by creating a Venn diagram of the three drug risk metrics (Figure 3.3). We observe that the main overlap occurs between the Beers Criteria and the ARS scale. The degree of overlap is very significant: 77.5% (480 out of 619) of those who had any anticholinergic risk according to the ARS score were also positive for a potentially inappropriate medication according to the Beers Criteria.

However, the 480 individuals with overlapping Beers and ARS criteria represented only 26% of the 1,835 total individuals who had a positive Beers criterion. These findings indicate that the Beers Criteria is able to detect a significant portion of pharmaceutical regimens' anticholinergic risk. Using a tool such as the ARS scale allowed us to identify about 8% more cases of drug risk than we would had found using the Beers Criteria alone.

The overlap between Beers Criteria and the Hines list of DDIs was also noteworthy. Out of the 81 total DDI cases identified by the Hines list, 41 (51%) were also captured by the Beers Criteria. Even though the total number of DDI cases was very small (about 2% of the total sample), the use of the Hines list allowed us to identify about 2% more cases of drug-related risk than we would have found if we had used the Beers Criteria alone.

There was minimal overlap between the results from the ARS and the Hines tools. Most of the overlap between these tools (13 out of 15 cases) was also picked up by the Beers Criteria.

Figure 3.3 Overlap between the different drug risk assessment tools



Note: percentages reflect the proportion of people taking at least one drug who fulfill each criterion. All persons taking at least one drug (n=4,196) are accounted for in the figure. ARS: anticholinergic risk scale; DDI: drug-drug interaction.

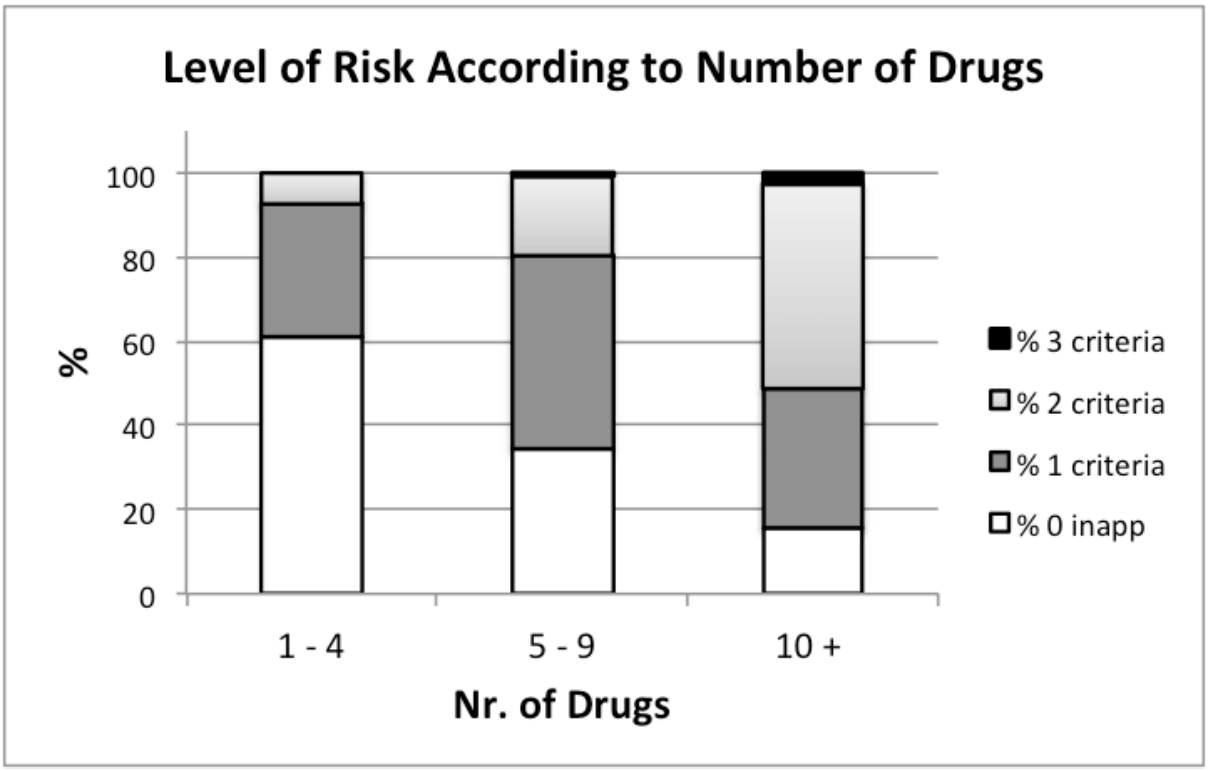
Relationship between number of drugs and level of drug risk

Most of the overlap between the tools occurred in persons who were using greater number of drugs (Figure 3.4). Among persons taking 1-4 drugs, 61% (n=1751) did not have any drug risk criteria; 32% (n=907) had one criterion; 7% (n=211) had two; and no persons had all three drug-risk criteria.

Among persons taking 5-9 drugs, 34% (n=414) did not have any drug risk criteria; 46% (n=555) had one criterion; 19% (n=227) had two; and 1% (n=10) had all three drug-risk criteria.

Among persons taking 10+ drugs, 16% (n=19) did not have any drug risk criteria; 33% (n=40) had one criterion; 49% (n=59) had two; and 2% (n=3) had all three drug-risk criteria.

Figure 3.4 Level of risk according to the number of drugs



Relationship between level of drug risk and individual characteristics

It is important to understand whether having greater number of drug risk criteria reflects a simple methodological issue of overlap between the tools, or whether greater number of drug risk criteria truly represent greater levels of risk.

Table 3.4 compares selected demographic, health status, health care utilization, and health behavior characteristics across different levels of drug risk as identified by the Beers Criteria, ARS scale and Hines list of clinically relevant DDIs.

Persons with greater levels of drug risk tended to be older, more frequently female, have poorer health and greater number of medical visits than persons with lower levels of drug risk. There was no difference in terms of preventative care, and in terms of race, religion, marital status, and socio-economic status (data not shown).

Taken together, these findings indicate that greater levels of drug risk as measured by the different tools do correlate with differences in health status. It is not possible to identify the extent to which (if at all) drug risk may be contributing to the observed differences in health status. Further research should be conducted to elucidate these associations.

Table 3.4 Relationship between drug risk levels and clinical characteristics

Variable Mean (sd)	No risk N=2,877	1 Criteria N=1,502	2-3 Criteria N=510	p-value
Demographic				
Age	73.07 (9.24)	73.54 (8.62)	74.70 (8.93)	0.0006
Female gender	0.57 (0.49)	0.65 (0.48)	0.73 (0.44)	<0.0001
Health Status				
Good self-reported health	0.53 (0.50)	0.34 (0.47)	0.33 (0.47)	<0.0001
Any chronic diseases	0.77 (0.42)	0.92 (0.26)	0.92 (0.27)	<0.0001
Nr. chronic diseases	1.62 (1.35)	2.40 (1.42)	2.70 (1.56)	<0.0001
Nr. of symptoms	1.29 (1.50)	1.77 (1.70)	2.18 (1.84)	<0.0001
Nr. ADLs with disability	1.50 (2.63)	2.30 (3.14)	3.23 (3.58)	<0.0001
Health Care Utilization				
Health insurance	0.42 (0.49)	0.41 (0.49)	0.49 (0.50)	0.0082
Medical visits last 12 months	4.97 (8.59)	6.82 (9.46)	9.29 (17.43)	<0.0001
Preventative exam last 24 mo.	0.48 (0.50)	0.49 (0.50)	0.51 (0.50)	NS
Health Behaviors				
Currently smoking	0.14 (0.34)	0.10 (0.30)	0.10 (0.29)	0.0008
Current alcohol use	0.32 (0.47)	0.24 (0.43)	0.20 (0.40)	<0.0001
Self-medication	0.27 (0.44)	0.30 (0.46)	0.34 (0.47)	0.001

Note: ADL: Activities of daily living.

3.4.2 Part 2 – Cross Sectional Analysis – Differences over Time

Across the three waves of the SABE study – 2000, 2006 and 2010 – there was a great increase in drug utilization. While a high number of participants (82%) was taking medicines in 2000, an even higher number (90%) was taking medicines in 2010. Theaverage number of drugs per person was about 2.7 drugs in 2000 and increased to about 4 drugs in 2010. The maximum number of drugs per person also increased, from 14 in 2000

to 17 in 2010. The frequency of polypharmacy more than doubled, from 18% to 40%, and the frequency of excessive polypharmacy quintupled from 1% to 5% over the 10-year period (Table 3.5).

The occurrence of drug risk, however, exhibited a different trend. In 2000, 43% of individuals had any form of drug risk ; in 2010, 39% of individuals had some form of drug risk. Most of this change was driven by a decline in the frequency of risk detected by the Beers Criteria. In 2000, 40% of participants had one or more Beers Criteria; in 2010, 35% of participants had one or more Beers Criteria. The average Beers score also declined, from an average of 0.54 criteria per person in 2000 to 0.44 criteria per person in 2010.

In fact, drug risk measured by the ARS scale and by the Hines list of clinically significant DDIs exhibited growth, not decline, over the 10-year period. Any anticholinergic risk went from 11% of the sample to 13% of the sample; the average ARS score increased from 0.27 to 0.36; and the presence of DDIs according to the Hines list went from 1% to 3% of the sample in this period.

As we discussed earlier, however, the relative contribution of the ARS and the Hines tools to the overall drug risk detection was very small. The largest component of risk detection in this sample was captured by the Beers Criteria, and so the decrease in the frequency of Beers-detected risk had a greater impact on the overall trend than the increases in the frequency of ARS- and Hines-detected risk.

Figure 3.5 displays a comparison between the increases in drug utilization and the increases in drug risk over time. Drug risk is presented as the proportion of cases with any risk criteria. While any utilization increased by about 1% a year, any risk decreased by about 0.4% a year. While polypharmacy increased by about 2% a year, the percentage of individuals with drug risk among those with polypharmacy grew at a slower rate, of about 1% a year.

While 77% of persons with polypharmacy (n=294 out of 382) had at least one risk criteria in 2000, 68% (n=279 out of 410) had at least one risk criteria in 2006 and 60% (n=321 out of 525) had at least one risk criteria in 2010.

These findings suggest that, although drug utilization grew significantly among older adults in Sao Paulo in the 10-year period, the type of drugs that individuals are taking is changing. Most specifically, older adults are less likely to be exposed to drugs deemed of "potential inappropriate use" by the Beers Criteria. This may not necessarily reflects changes in prescription practices. In Brazil, many drugs may be purchased without a medical prescription. Hence, there may be other drivers, such as cultural preferences, availability of drugs in the market, drug prices, and others, that may be contributing to the shift on the types of drugs being used by the Sao Paulo older adult population.

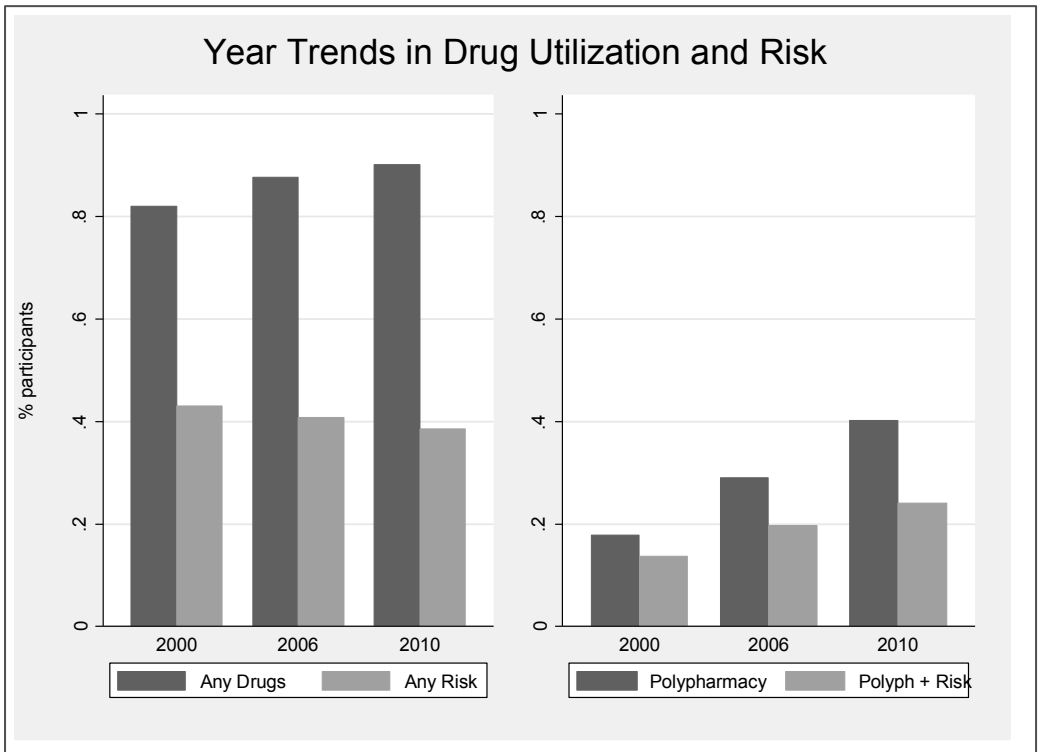
In addition, the reduction is not occurring across all dimensions of drug risk. The two other tools that we utliized identify relatively small, but important increases in the occurrence of anticholinergic risk and drug interactions over time. These sources of risk, although less frequent than the inappropriateness captured by the Beers Criteria, are also clinically relevant and should not be ignored.

Table 3.5 Trends in drug utilization and drug risk across the SABE survey waves

Variable Mean (sd)	Year 2000 N=2143	Year 2006 N=1413	Year 2010 N=1333	p-value
Drug Utilization				
Any drugs	0.82 (0.38)	0.88 (0.33)	0.90 (0.30)	<0.0001
Avg. nr. drugs	2.67 (2.19)	3.34 (2.55)	4.09 (2.97)	<0.0001
Nr. drugs, range	0 - 14	0 - 15	0 - 17	
Polypharmacy	0.18 (0.38)	0.29 (0.45)	0.40 (0.49)	<0.0001
Excessive polyph.	0.01 (0.09)	0.03 (0.16)	0.05 (0.22)	<0.0001
Drug Risk				
Any risk criteria	0.43 (0.50)	0.41 (0.49)	0.39 (0.49)	0.0319
1 Criteria	0.34 (0.47)	0.30 (0.46)	0.27 (0.44)	0.0001
2 Criteria	0.09 (0.29)	0.10 (0.31)	0.11 (0.32)	0.0007
3 Criteria	0.00 (0.02)	0.00 (0.07)	0.00 (0.07)	0.0312
Any BEERS Criteria	0.40 (0.49)	0.36 (0.48)	0.35 (0.48)	0.0035
BEERS score	0.54 (0.76)	0.47 (0.72)	0.44 (0.69)	0.0005
Any ARS drug	0.11 (0.32)	0.14 (0.35)	0.13 (0.34)	0.0429
ARS score	0.27 (0.83)	0.35 (1.03)	0.36 (1.01)	0.0061
Any DDI	0.01 (0.10)	0.02 (0.13)	0.03 (0.16)	0.0016

Note: polypharmacy: five or more prescription or over-the counter drugs; excessive polypharmacy: ten or more prescription or over-the counter drugs; ARS: anticholinergic risk scale; DDI: drug-drug interaction. p-values and were calculated by F-tests in linear regressions of each variable on indicators for the three years.

Figure 3.5 Year trends in drug utilization and risk



Note: The table presents a comparison between the proportion of individuals in the SABE study that had any drug utilization and the proportion of persons with any drug use who also had any drug risk criteria (left); and a comparison between the proportion of individuals in the SABE study that had polypharmacy and the proportion of persons with polypharmacy who also had any drug risk criteria (right).

Drug Utilization Trends by Therapeutic Class

In order to contribute to elucidating the trends in drug risk that we described in the previous section, we explore the drugs most commonly utilized among our sample in each of the survey waves. First, we examine the different therapeutic drug classes according to the WHO-ATC classification (Table 3.6). We also explore trends in the underlying health conditions that might require such drugs. We describe chronic disease trends in the next section.

The drug classes that exhibited the most significant increases were drugs related to the cardiovascular system (WHO-ATC category C), which increased from 0.94 to 1.61 drugs per person in the 10-year period. The second largest increase occurred among drugs related to the alimentary tract and metabolism (WHO-ATC category A), which increased from 0.49 to 0.88 drugs per person; and the third largest increase was among drugs related to

the nervous system (WHO-ATC category N), which increased from 0.45 to 0.61 drugs per person in the 10-year period.

The use of systemic hormonal preparations, excluding sex hormones and insulin (WHO-ATC category H) increased from 0.04 to 0.16 drugs per person; and drugs related to the sensory organs (drugs for ophthalmic and otologic use, WHO-ATC category S) increased from 0.05 to 0.10 drugs per person in the period.

No drug class had decreases in utilization over time. Drugs related to the blood and blood forming organs, dermatologic drugs, genito-urinary system and sex hormones, anti-infective, antineoplastic and immunomodulating agents, drugs related to the musculo-skeletal system, anti-parasitic products, drugs related to the respiratory system, and miscellaneous drugs did not exhibit significant trends over time among the study participants.

Table 3.6 Drug utilization trends by WHO-ATC therapeutic class

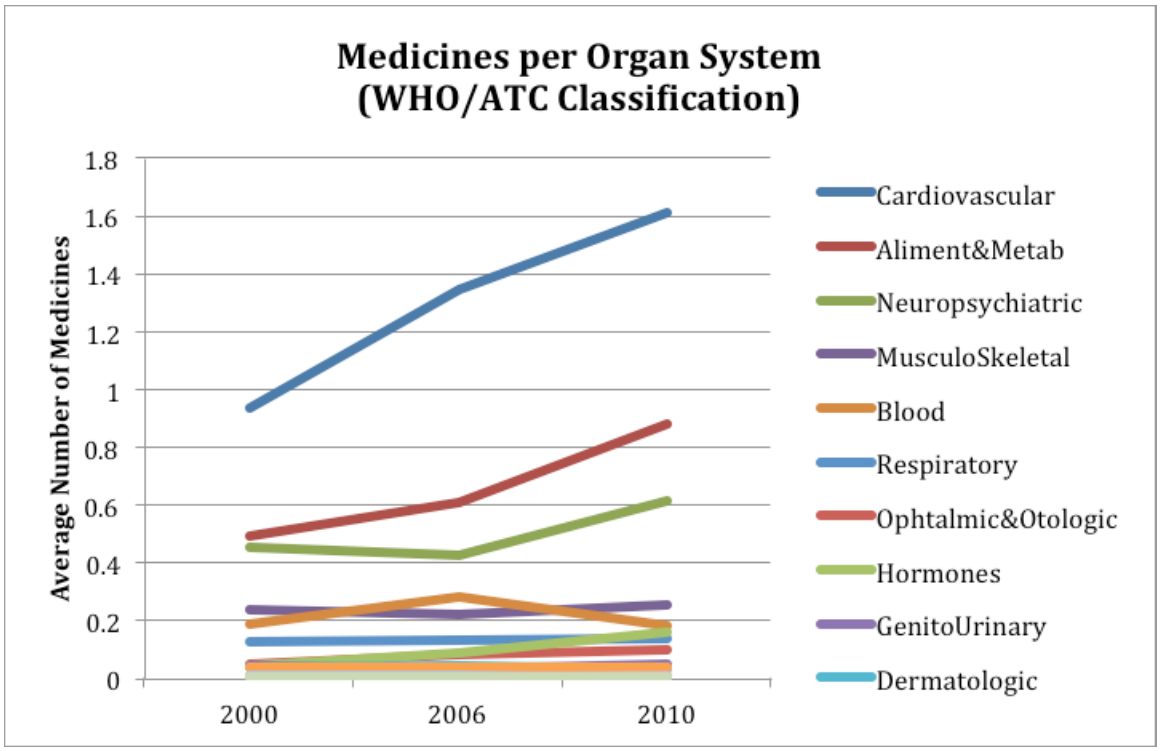
Nr. Drugs WHO Category Mean (sd)		Pooled N=4889	Year 2000 N=2143	Year 2006 N=1413	Year 2010 N=1333	p-value
A	Aliment-Metabol	0.63 (0.93)	0.49 (0.80)	0.61 (0.90)	0.88 (1.08)	<0.0001
B	Blood	0.21 (0.44)	0.19 (0.42)	0.28 (0.49)	0.18 (0.42)	<0.0001
C	Cardiovascular	1.24 (1.32)	0.94 (1.12)	1.35 (1.31)	1.61 (1.49)	<0.0001
D	Dermatologic	0.04 (0.23)	0.04 (0.23)	0.04 (0.24)	0.03 (0.21)	NS
G	Genito-Urinary	0.04 (0.21)	0.04 (0.22)	0.03 (0.18)	0.05 (0.23)	NS
H	Hormones	0.09 (0.30)	0.04 (0.21)	0.09 (0.29)	0.16 (0.39)	<0.0001
J	Antiinfectives	0.04 (0.21)	0.04 (0.21)	0.04 (0.21)	0.04 (0.22)	NS
L	Antineoplastics	0.01 (0.10)	0.01 (0.09)	0.01 (0.08)	0.01 (0.12)	NS
M	Musculo-Skeletal	0.24 (0.51)	0.24 (0.51)	0.22 (0.48)	0.26 (0.53)	NS
N	Nervous System	0.49 (0.78)	0.45 (0.73)	0.43 (0.77)	0.61 (0.87)	<0.0001
P	Antiparasitic	0.01 (0.08)	0.01 (0.08)	0.01 (0.08)	0.00 (0.07)	NS
R	Respiratory	0.13 (0.46)	0.13 (0.44)	0.13 (0.48)	0.14 (0.48)	NS
S	Sensory	0.07 (0.36)	0.05 (0.28)	0.08 (0.40)	0.10 (0.42)	0.0001
V	Various	0.01 (0.09)	0.01 (0.10)	0.01 (0.12)	0.00 (0.05)	0.0348

Note: contents represent average number of drugs per person among the pooled SABE sample (left) and in each of the study waves. p-values calculated by F-tests in linear regressions of each variable on indicators for the three years. "Sensory" drugs are those for ophthalmic and otologic use.

Figure 3.6 displays the trajectories of each WHO-ATC therapeutic class across the study periods, so that the relative patterns of change across classes can be visualized. Although drugs related to the cardiovascular system,

the alimentary tract, and the nervous system exhibited utilization increases over time, the magnitude of the change and the levels of utilization were far more marked among drugs related to the cardiovascular system. This pattern may reflect the epidemiologic changes in our sample that we describe below.

Figure 3.6 Drug utilization trends by WHO-ATC therapeutic class



Epidemiologic Trends – Prevalence and Type of Chronic Diseases

We examined the trends in the chronic disease diagnoses among our sample (Table 3.7) in order to explore whether any corresponding disease patterns could be identified. Overall, the prevalence and number of chronic diseases increased significantly during the time period.

About 79% of participants had a chronic disease in 2000, and 87% had a chronic disease in 2010 (of note, the same percentage of individuals reported a chronic disease in 2006). The average number of chronic diseases per participant increased from 1.69 to 2.19 during the period.

None of the chronic diseases examined by the SABE study exhibited a significant decrease in prevalence over time. Hypertension increased from an average of 54% to an average of 68% of the sample; diabetes increased

from 17% to 25%; neuropsychiatric conditions increased from 14% to 23%; joint diseases increased from 29% to 34%; and osteoporosis increased from 15% to 21%.

There was also a reported increase in cancer, from 4% to 8% of the sample. Health disease, lung disease, and stroke had stable rates across the three time periods.

Table 3.7 Chronic disease trends in the SABE study

Variable Mean (sd)	Pooled N=4889	Year 2000 N=2143	Year 2006 N=1413	Year 2010 N=1333	p-value
Any NCDs	0.84 (0.37)	0.79 (0.40)	0.87 (0.34)	0.87 (0.34)	<0.0001
Nr. NCDs.	1.97 (1.46)	1.69 (1.31)	2.19 (1.53)	2.19 (1.53)	<0.0001
Chronic Diseases					
Hypertension	0.61 (0.49)	0.54 (0.50)	0.64 (0.48)	0.68 (0.47)	<0.0001
Diabetes	0.20 (0.40)	0.17 (0.37)	0.21 (0.41)	0.25 (0.43)	<0.0001
Heart Disease	0.23 (0.42)	0.20 (0.40)	0.25 (0.43)	0.24 (0.43)	0.0005
Lung Disease	0.10 (0.31)	0.10 (0.30)	0.12 (0.32)	0.09 (0.29)	NS
Stroke	0.08 (0.28)	0.08 (0.27)	0.09 (0.29)	0.08 (0.28)	NS
Cancer	0.05 (0.23)	0.04 (0.19)	0.06 (0.23)	0.08 (0.27)	<0.0001
Neuropsychiatric	0.20 (0.40)	0.14 (0.35)	0.24 (0.43)	0.23 (0.42)	<0.0001
Joint Disease	0.32 (0.47)	0.29 (0.45)	0.36 (0.48)	0.34 (0.47)	<0.0001
Osteoporosis	0.20 (0.40)	0.15 (0.36)	0.25 (0.43)	0.21 (0.41)	<0.0001

Note: contents represent average chronic disease rates among the pooled SABE sample (left) and in each of the study waves. NCDs: chronic non-communicable diseases. p-values calculated by F-tests in linear regressions of each variable on indicators for the three years.

The chronic disease trends largely correspond to the trends in utilization described for the multiple drug classes. The most frequently prescribed drug classes (cardiovascular, metabolic, and neuropsychiatric drugs) matched the most commonly reported chronic diseases (hypertension, diabetes, and neuropsychiatric conditions).

The increase in the reporting of cancer was not accompanied by increased report of anticancer drugs. This may be due to the nature of the survey question, which asked participants if they had ever been diagnosed with each of the chronic conditions. Therefore, the rates described here may not necessarily reflect active disease. The reporting of cancer may reflect historical as well as current cases.

Of note, the increase in reporting of joint disease and osteoporosis did not seem to be accompanied by increases in the use of musculo-skeletal drugs.

There was agreement in the mostly stable trends of respiratory diagnoses and drug utilization. Other conditions such as those affecting sensory organs and hormones were not inquired in the survey.

Drug risk trends according to the risk assessment tools

As previously described, a decrease in the frequency of Beers-detected drug risk was observed across the survey waves. Below we plot the trajectory of the eight most frequently utilized drugs across all the survey waves (Figure 3.7). Diclofenac, nifedipine, methyldopa, chlorpropamide, and orphenadrine, which were among the most frequently utilized drugs in 2000, exhibited dramatic declines in utilization across the three survey waves. A less marked, but significant increase in utilization occurred for amitriptyline, doxazosin, and ibuprofen in this period.

Figure 3.7 Drug utilization trends according to the Beers Criteria

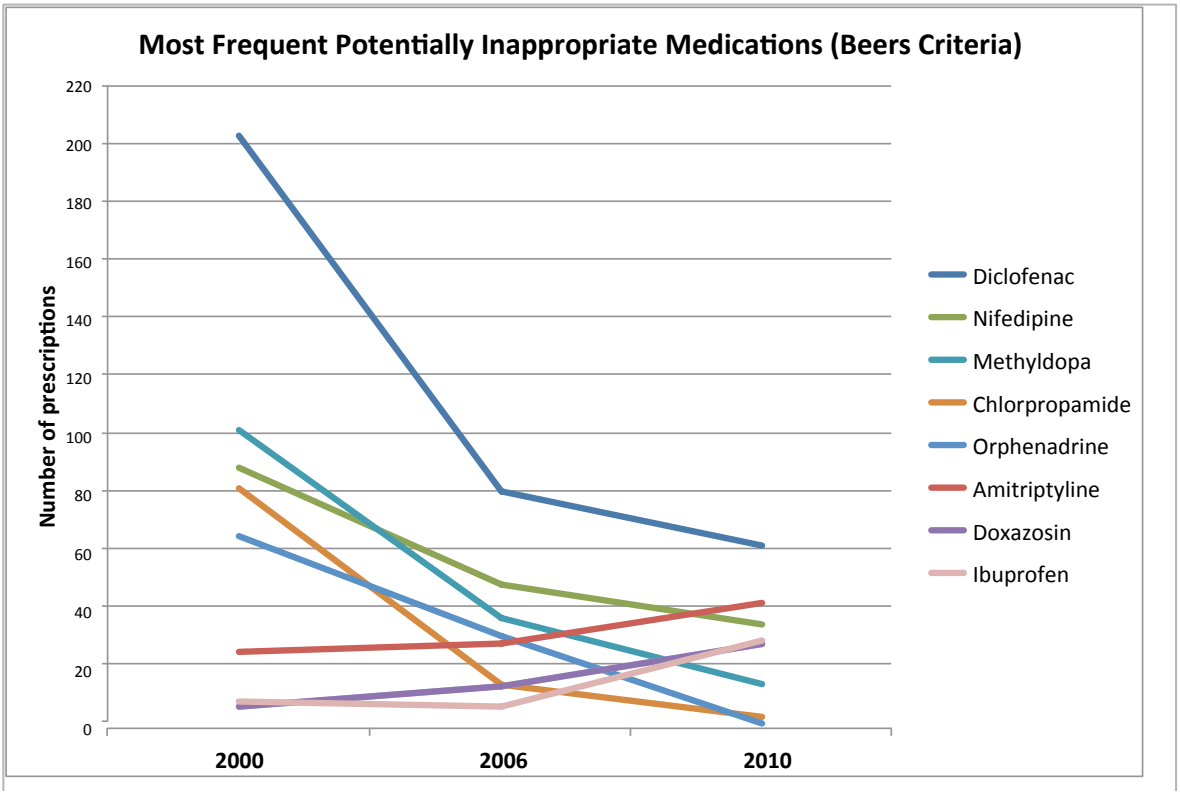


Table 3.8 displays the 15 most commonly utilized drugs that are identified as potentially inappropriate for the older adult population according to the Beers Criteria. This table identifies additional patterns such as reductions in estrogen, dexclorpheniramine, and a stable use of carisoprodol

Table 3.8 Utilization trends of potentially inappropriate drugs

Drug Code	Drug Name	2000	2006	2010	pooled
M01AB05	Diclofenac	203	80	61	344
C02AB01	Glibenclamide	85	88	100	273
C08CA05	Nifedipine	89	49	35	173
A10BB01	Amiodarone	69	50	43	162
A10BB02	Methyldopa	102	37	14	153
C01BD01	Chlorpropamide	82	14	3	99
M03BC51	Orphenadrine	66	31	1	98
N05BA01	Amitriptyline	26	29	43	98
G03C	Diazepam	38	23	23	84
R06AB52	Carisoprodol_Combinations	31	20	32	83
M03BA52	Estrogens	35	12	21	68
N06AA09	Dexchlorpheniramine_Combinations	33	20	9	62
M01AC01	Doxazosin	7	14	29	50
N03AE01	Clonazepam	25	22	0	47
N05BA06	Ibuprofen	9	7	30	46

Note: colors represent drugs that were among the 10 most frequently utilized in the corresponding year (light brown= 2000, dark brown=2006, orange=2010); and the 15 most frequently utilized in the pooled sample (blue).

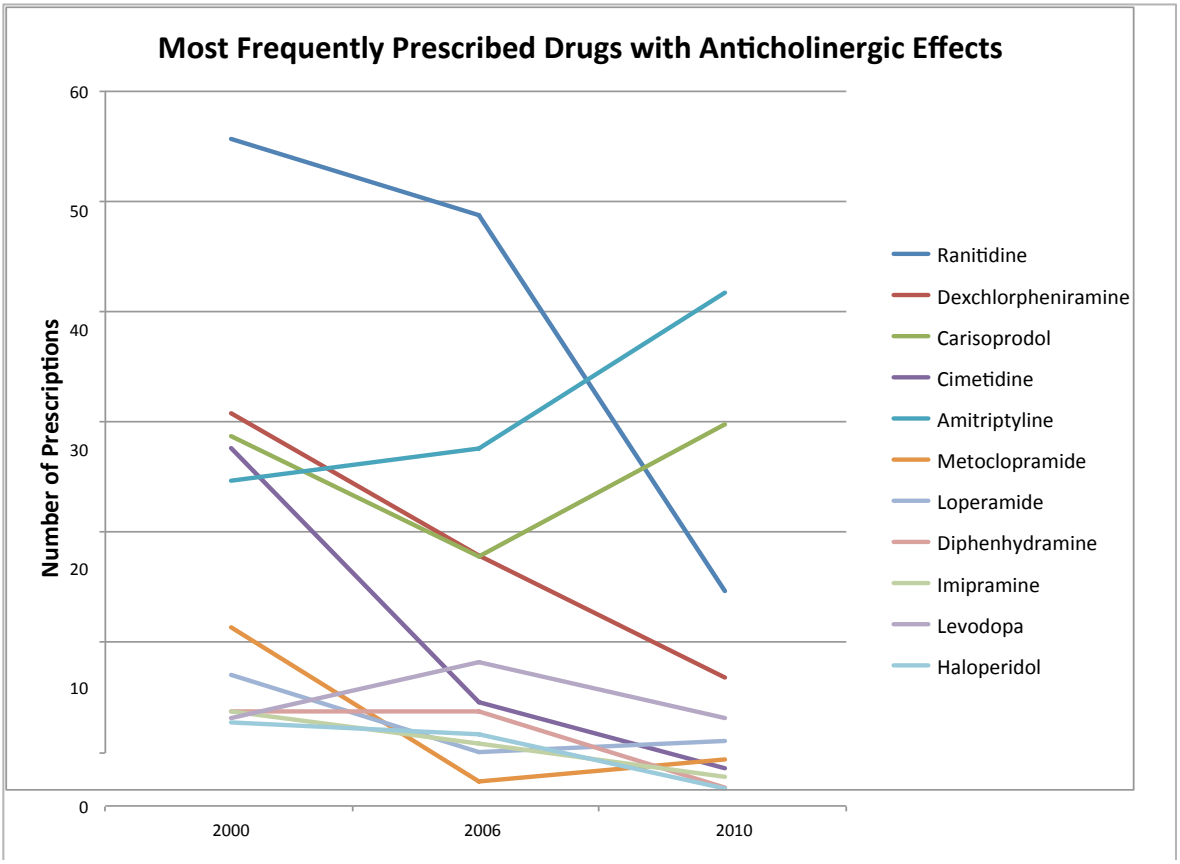
We also examine the utilization patterns for drugs with anticholinergic effects (Figure 3.8). Among the most commonly utilized drugs with anticholinergic potential, most drugs exhibited decreasing or stable utilization trends over time.

Ranitidine, cimetidine, metoclopramide and dexclorpheniramine exhibited marked decreases in utilization. Diphenidramine, loperamide, haloperidol, imipramine, and levodopa also exhibited decreased utilization. Carisoprodol was relatively stable, although with fluctuations, over time.

The only ARS drug that exhibited a utilization increase over time was amitriptyline. It is possible that other, less frequently used drugs, drove the increase in ARS risk verified in the SABE sample over time.

Three of the most frequently used ARS drugs were also captured by the Beers Criteria: amitriptyline, carisoprodol and dexclorpheniramine. This exemplifies some of the overlap that we identified earlier.

Figure 3.8 Drug utilization trends according to the ARS scale



3.5 DISCUSSION

This study contributed to the understanding of the association between drug utilization and drug risk among older adults in Sao Paulo, Brazil.

We found that drug risk is frequent, and is strongly associated with taking higher number of drugs per day. Drug risk was a special concern among persons with polypharmacy. About two-thirds of people with polypharmacy were exposed to some form of drug risk, and the risk increased with higher numbers of drugs in a pharmaceutical regimen. The composition of drug treatments followed the patterns of the underlying health conditions reported by the participants. We did not find a specific group of drugs or drug combinations associated with most of the drug risk associated with polypharmacy.

These findings suggest that the association between polypharmacy and drug risk should receive greater attention from public health decision-makers in Sao Paulo, and that public health interventions aimed at reducing drug risk should target all older adults with polypharmacy.

Improving the level and the quality of monitoring of persons with polypharmacy might help promote early detection and better management of drug risk. Developing therapeutic guidelines that recommend periodic review of pharmaceutical regimens for all older adults with polypharmacy could help raise providers' awareness and help change prescribing behaviors. Drug reviews would provide an opportunity to improve health care integration across multiple prescribers and increase prescribers' accountability. Other strategies to raise providers' awareness of the association between polypharmacy and drug risk – "Dear Doctor" letters, for example - could be implemented by the regulatory agency, the Ministry of Health, or professional associations, and could help change prescribing and improve monitoring.

It is important to raise awareness about the association between polypharmacy and drug risk for the public as well. Public awareness campaigns could be carried out either on the general media or in more targeted outlets such as pharmacies. Raising awareness could motivate older adults with polypharmacy to discontinue self-prescribed drugs and to request better monitoring from their providers. Lastly, raising awareness might help patients contribute to health care integration by providing more complete drug information when they seek multiple providers.

We found that higher levels of drug risk were associated with worse health – higher comorbidities, higher disability, more clinical symptoms, and worse self-reported health status – in our sample. Our study could not address whether there were any causal links between drug risk and poor health status. It is possible that drug risk might have contributed to participants' worse health status. It is also possible that both drug risk and worse health might have been driven by a common cause such as underlying chronic diseases. The medical literature indicates that both mechanisms are possible, and so further studies to elucidate the relationship between drug risk and poorer health among Brazilian older adults are needed. It is important that these studies control for the effect of the underlying health conditions that motivated the use of drugs in the first place.

Drug risk was present in a significant proportion of individuals who took few (four or less) drugs a day. Because of the association with worse health, drug risk should remain a matter of concern even among people without polypharmacy.

Our study found that, even though the frequency of drug utilization and the frequency of polypharmacy increased sharply in the 10-year interval, the overall drug risk levels exhibited a decline. Drug risk decreased both among the overall sample and among persons with polypharmacy in this period.

Similar findings were described in the context of French older adults (Bongue et al., 2009). These investigators concluded that changes in prescription practices were the main underlying driver. In Brazil, however, not all drugs require a medical prescription. Many of the drugs used to treat chronic conditions are in fact over-the-counter. Therefore, drug choices may be subject to a greater variety of influences in Brazil, and this should be taken into consideration by future investigations.

The decrease in drug risk identified in our sample was largely driven by a reduction in drug inappropriateness as measured by the Beers Criteria. Anticholinergic risk detected by the ARS scale and DDIs detected by the Hines list actually increased in the study period. It is important to understand what drove these differences. The trajectories of specific drugs or drug classes may provide useful insights to understand drivers of utilization and prescription patterns. We found that some particular drugs – diclofenac, nifedipine, methyldopa, and others - drove most of the decline in drug risk. Future investigations may gain more insights if they focus on such drugs to understand which factors motivated their reduction.

The Beers Criteria captured most of the persons with drug risk identified by the ARS scale the Hines list of DDIs in our sample. Still, we recommend against using the Beers Criteria as the single tool to identify drug risk in similar population-level studies. Individuals with multiple risk criteria tended to have worse health than those with only the Beers Criteria in our study. Examining multiple dimensions of drug risk helps identify individuals who may be at greater risk of poorer health outcomes. Assessing a single metric of drug risk may mislead public health decision-making and may prevent some particularly serious forms of drug risk, such as drug interactions and anticholinergic symptoms, from being identified.

Our study had several limitations. First, the data that we utilized was collected by a household survey whose main goal was to investigate health dimensions not related to drug utilization. Nevertheless, the study collected comprehensive information on drug use, both via self-report and via direct observation of pill boxes. The use of WHO-ATC codes to record the drugs greatly contributed to data quality. Given the particularities of the Brazilian context, a survey may be the best source of information on drug use.

Private insurance does not cover outpatient drugs in Brazil; hence, administrative claims data are not available. Drugs are purchased out-of-pocket, so pharmacy claims data are also not available. Many individuals obtain drugs from the public system. However, only drugs from a selected formulary are provided by the public health system. Any data from public drug provision would not capture the totality of drugs utilized by the population. Electronic health records are proprietary of certain health providers or insurers; they may not capture drugs that were self-prescribed or that were prescribed by out-of-network providers. Even if they were available, none of these sources would likely be representative of the total population of older adults in Sao Paulo, which was another strength of our data.

Our study did not have information on drug dosage and posology. This prevented us from addressing issues of drug toxicity. However, drug toxicity is not a frequent source of drug risk (Edwards & Aronson, 2000). Most of the drug risk assessment tools available in the medical literature do not take drug dosage into consideration. It would be very important to develop tools that could comprehensively assess drug risks taking into consideration not only the drug dosage and posology, but also a more comprehensive picture of a person's clinical characteristics such as underlying health conditions and metabolic capacity. Such comprehensive tools would be a valuable contribution to clinical practice and to efforts towards to personalized medicine.

We utilized only the part of the Beers Criteria that applied to the general older adult population. We did not examine disease-specific drug risks. While this approach allows for the evaluation of drug risk patterns among the general older adult population, it assumes that the risks from the examined drugs are independent from the underlying health conditions that a person may have.

A limitation of this approach is that this assumption may not hold in all situations. An individual with an underlying health condition that is particularly sensitive to anticholinergic drug adverse effects may have a

different burden from a given ARS drug than another person without underlying health conditions. However, having looked at the interaction between drugs and diseases would have addressed a different research question than the one that we set up to explore. The level of granularity required for the investigation of drug and disease associations would have been better addressed by studies that focus on a particular condition, for example, diabetes, or on a particular drug class.

More comprehensive investigations would also have required specialized software systems, for example for a comprehensive analysis of drug interactions. Our use of a list-based tool to identify drug interactions has likely limited our ability to detect DDIs in our study population, and so our findings may have underestimated the true occurrence of DDIs among Sao Paulo older adults. However, most cases of DDIs among that population are of mild or moderate clinical significance (Secoli, 2010), and those were not the primary goal of our study. We were primarily interested in identifying cases of severe clinical risk. The Hines list identifies a set of DDIs that are associated with hard clinical outcomes such as death and hospitalization. Therefore, it was likely an appropriate tool for our goal.

Our methods are in line with several recent investigations of drug utilization in other settings, which have mostly employed the Beers Criteria (Baldoni, 2012; Koyama, 2013; Kaufman, 2014). By introducing additional tools to capture additional dimensions of drug risk we empirically demonstrated the importance of a comprehensive drug risk assessment in population studies. Better tools that combine these and other dimensions of drug risk are necessary, especially to improve drug risk evaluations at the population level.

4. CHAPTER IV: INDIVIDUAL AND COMMUNITY FACTORS ASSOCIATED WITH POLYPHARMACY IN OLDER ADULTS: A MULTI-LEVEL ANALYSIS

ABSTRACT

Background: Polypharmacy exposes individuals to increased risk of drug-related problems and negative clinical outcomes. Older adults are especially vulnerable. Not all polypharmacy may be explained by clinical need. It is possible that characteristics at the community level may influence polypharmacy independently of individual characteristics. Understanding the main factors associated with polypharmacy is important in order to devise potential policy targets.

Aims: This study investigated the occurrence of polypharmacy among older adults in Sao Paulo, Brazil's largest city and main economic center. We aimed to identify time trends and geographic variation in polypharmacy and inappropriate polypharmacy, as well as individual and community-level characteristics associated with their use.

Method: We implemented multi-level latent variable and mixed-effects models combining data from a household survey of non-institutionalized older adults living in Sao Paulo – the SABE study – with community data from official public sources. The SABE study surveyed a representative sample of the Sao Paulo non-institutionalized population 60 years and older in 2000, 2006 and 2010. We defined "communities" as the 31 administrative areas in which Sao Paulo is divided and where the participants lived. We defined polypharmacy as the use of five or more drugs per day, and inappropriate polypharmacy as polypharmacy combined with at least one drug risk criterion.

Results: The prevalence of polypharmacy and inappropriate polypharmacy among older adults doubled over the 10-year period. A very small portion (about 2%) of the variation in polypharmacy was associated with living in a given community. Individual-level factors were the most associated with polypharmacy – worse health, higher age, female gender, and higher health care utilization. Having private health insurance was not associated with

polypharmacy, but living in areas with higher insurance coverage was associated with higher odds of polypharmacy even after controlling for individual-level factors. Higher socio-economic status at the community level and higher older adult mortality were also independently associated with increased odds of polypharmacy. The investigation of inappropriate polypharmacy had similar findings.

Conclusion: Polypharmacy and inappropriate polypharmacy are increasing in Sao Paulo older adults. It is likely that they are mainly driven by individual characteristics. However, our findings indicate an independent role of community factors such as health status and economic resources that should be further investigated.

4.1 INTRODUCTION

4.1.1 Policy Problem: Exposure to Polypharmacy and Inappropriate Polypharmacy

Polypharmacy, the excessive use of prescription drugs, is a growing worldwide phenomenon, especially among older adults. There is no consensus among clinical communities regarding how many drugs are too many. In general, a threshold of five or more drugs is used because it has been shown to correlate with an increased risk of adverse effects and mortality.

Polypharmacy exposes individuals to increased risk of drug adverse effects as well as negative clinical outcomes such as falls, frailty, cognitive impairment and mortality. Older adults are especially vulnerable, as they tend to be prescribed more drugs, and they to have less metabolic reserve with which to process pharmaceuticals. Problems with care coordination may result in drugs being prescribed without appropriate monitoring, compounding risks without adding benefits. Depending on the insurance benefits, polypharmacy may use up financial resources, which can be especially burdensome for older adults, who generally have fixed incomes.

Polypharmacy may result from the need to treat increasingly frequent and multi-factorial chronic conditions. Other characteristics such as a person's higher income and educational levels, and higher tendency to seek physician care, have been shown to affect polypharmacy even when controlling for chronic conditions. In addition, characteristics of the areas where individuals live and seek care may exert influence in the propensity for polypharmacy independently of personal characteristics.

Because public resources are often spent to provide older adults' drug treatments, polypharmacy is also a matter of appropriate management and rational use of public resources. These questions are especially relevant in the context of low-and middle-income countries like Brazil, where the demands of rapidly growing aging populations pose significant burden on public health systems, but where scarce resources are divided between multiple sources of disease burden such as maternal-child conditions, infectious disease and other critical needs.

In this study, we examine the phenomenon of polypharmacy among older adults living in Sao Paulo, Brazil. We explore temporal trends in polypharmacy over a period of 10 years, and we investigate the association between polypharmacy and multiple factors at the individual and at the community level. In addition, we investigate the occurrence of inappropriate polypharmacy among this population. We define inappropriate polypharmacy as the cases where, in addition to being with polypharmacy, individuals also have some form of objectively measured drug risk.

Our main objective is to provide evidence to support public health decision-making to mitigate the growing problem of polypharmacy, and especially the burden from inappropriate polypharmacy, in the context of Sao Paulo.

4.1.2 Background

Latin American countries in general, and Brazil in particular, have experienced fast population aging rates (A. Palloni et al., 2002). The prevalence of chronic diseases is growing significantly in LMICs, and some diseases such as diabetes have higher prevalence in Brazil than in other countries of the region (A. Palloni & McEniry, 2007).

Chronic conditions often require combined pharmaceutical approaches for their appropriate management. Their pathophysiologic mechanisms tend to be multi-factorial, and these conditions tend to occur in patterns of multiple comorbidities. Pharmaceuticals are needed not only as treatments, but also as prevention – either primary or secondary – of these conditions.

It is clear there are patient circumstances that will determine the need for certain drugs. Studies have also shown, however that other factors aside of need may influence can influence the number of drugs prescribed. The main examples are the availability and type of insurance, and the prescribing preferences and practices of health care providers (Cutler et al., 2013).

A cultural model where patients expect and doctors deliver “a pill for every ill” has been described among many patients and health providers (Busfield, 2010). Many scholars have also described a growing tendency of

prescribers to medicalize symptoms that are not inherently pathological but that are part of the life cycle. This phenomenon has been called the "pharmaceuticalization" of health (J. G. Biehl, 2007; Davis, 2015; Williams, Martin, & Gabe, 2011), and it has been described to affect conditions across the life spectrum – from attention deficit disorders in childhood, to pre-menstrual syndrome in early adulthood, and to menopause in later life, for example. In older ages, it is possible that "pharmaceuticalization" of health may contribute to polypharmacy through the prescription of unnecessary drugs to address symptoms that are not pathological, but are part of the aging process.

In the Brazilian context other factors may contribute to greater exposure to polypharmacy independently of need. The context of Brazil has two main singularities: first, access to "prescription" drugs does not always require a prescription. With the exception of controlled substances such as mental health treatments, opioids, and antimicrobial drugs, most drugs to treat chronic diseases can be purchased over the counter without a written medical prescription in Brazil. This is in accordance with national regulations and is a widespread practice. Because a prescription is not necessarily required in order to maintain treatments, access to care may affect polypharmacy primarily via greater drug initiation. Persons with greater access to care may have their conditions diagnosed earlier and more often than persons without access to care, so that they know which treatments they need. About two-thirds of medical visits in Brazil result in a prescription (Boing, Bertoldi, & Peres, 2011). However, persons with lower access to care may lack opportunities for appropriate monitoring and follow-up, which may in turn result in fewer opportunities to discontinue unnecessary drug treatments.

In Brazil, the availability of private pharmacies may play a significant role in enabling the continuation of polypharmacy. Because obtaining current medical prescriptions is not a requirement for continued drug utilization, the role of private pharmacies with polypharmacy is likely to be independent from health services utilization.

Second, the type of service (public or private) matters. As a result of longstanding national regulations private insurance plans do not cover outpatient drugs in Brazil.[13] Drugs for outpatient use are mostly purchased in the

[13] Regulations changed in 2015 to accommodate for the provision of oral cancer treatments. This recent change is limited to one drug class and has been incorporated to varying extents by the insurance companies. Also, it occurred after our data was collected, so we do not expect that it could influence our results or interpretation.

private market by out-of-pocket payments. The government provides drugs free of cost to individuals who cannot afford to purchase drugs in the private market. However, public provision of drugs is limited to a national formulary.[14] Drugs provided in the public system are dispensed only in public pharmacies and typically require medical prescriptions that must be current and must be issued by a public health service (Secretaria de Políticas de Saúde, 2000).

Because of the different requirements and administrative procedures, it is likely that the relationship between health care access and drug provision is different between the private and the public sectors in Brazil. It is also possible that providers working in the public and in the private systems may have different prescribing preferences and practices. For example, public providers may be more limited in their prescriptions if they restrict their options to those that are part of national formularies (Boing, Bertoldi, Boing, Bastos, & Peres, 2013). Private providers may be more aggressive in prescribing drugs and may be more likely to "pharmaceuticalize" normal aging processes (Williams et al., 2011).

In addition, the Brazilian economy has significantly developed in recent years and the pharmaceutical market has greatly expanded; several governmental policies to increase access to medicines have been implemented; and average incomes have increased, allowing families to purchase more medicines in the private market (Branco, 2010). These factors may have contributed to polypharmacy, and not only by helping individuals access the treatments they need. When drugs become more accessible, there is less incentive to discontinue ongoing treatments once they become unnecessary.

Fragmentation of care and lack of care coordination may also contribute to polypharmacy by not providing adequate monitoring of ongoing treatments. Multi-drug regimens, especially polypharmacy, pose great challenges in terms of detecting and managing drug risks. In the Brazilian setting it has been demonstrated that patients may remain on contra-indicated drugs for long periods of time even after an adverse effect has been detected (Barbosa et al., 2006).

[14] The provision of medicines is shared between federal, states and local governments. Some states and municipalities can complement the national formulary by adding drugs to their regional or local formularies (Ministério da Saúde, 2000).

Even drugs that have been prescribed for an appropriate indication, at the appropriate doses and for the appropriate duration may cause harm. Prescribing polypharmacy without appropriate clinical monitoring may make it difficult to identify an adverse effect when it occurs. If an adverse effect goes undetected, new drugs may be prescribed to treat it without discontinuing the offending drug. This "prescribing cascade" is often associated with polypharmacy and may have serious clinical consequences.

In order to mitigate the risks associated with polypharmacy, it is important to first understand which factors are associated with its use. Most of the literature on the determinants of polypharmacy indicates that persons of older ages (Franchi et al., 2013; Hovstadius, Hovstadius, et al., 2010; Jiménez Herrera & Fernández Rojas, 2008; Linjakumpu et al., 2002; Nobili et al., 2011), of the female gender (Cashion et al., 2015; Perry & Turner, 2001), with higher number of chronic diseases (Chan et al., 2009; Jiménez Herrera & Fernández Rojas, 2008; Jyrkka et al., 2009a; Kim et al., 2014), and with greater disability (Chan et al., 2009) tend to have more polypharmacy. In addition, persons with multiple providers, supplemental health insurance, and greater levels of physician visits are more likely to have polypharmacy (Kim et al., 2014). Understanding the determinants associated with polypharmacy important in order to devise potential targets for policies aimed at mitigating its use.

Geographic variation studies have demonstrated that health care utilization varies dramatically across regions, and not fully explained by the needs of the underlying populations (Cutler et al., 2013; Fisher et al., 2003a, 2003b; J. Wennberg & Gittelsohn, 1973; Zuckerman et al., 2010). Some factors that occur at the geographic-area level may also influence polypharmacy in addition to the individual characteristics described above. It has been demonstrated that living in urban and metropolitan areas (Jiménez Herrera & Fernández Rojas, 2008) and areas with higher income (Perry & Turner, 2001) were associated with increased likelihood of polypharmacy even after controlling for individual characteristics. Geographic variation in polypharmacy has also been described in Brazil, in association with higher area-level income (Coelho Filho et al., 2004).

In this study we investigate the occurrence and the determinants of polypharmacy in the context of Sao Paulo, the largest city of Brazil and its major economic center.

Sao Paulo is a city of country-size proportions, both in terms of population and economic production. Its population of over 11 million inhabitants is larger than countries such as Belgium and Bolivia. Sao Paulo would represent the world's 77th largest population if it were a country (Factbook, 2010). There is great heterogeneity across the multiple geographic areas of Sao Paulo. The richest, and arguably also the poorest people in Brazil live there. Because of its gigantic proportions the administration of Sao Paulo is divided between 31 sub-prefectures, which are in charge of most public works at the local level, including the delivery of health care through the public health system.

There is evidence that the population of older adults in Sao Paulo is exposed to polypharmacy and has a high drug risk potential (Secoli et al., 2010). The Sao Paulo population is progressively aging, and so the occurrence of polypharmacy is expected to increase. In addition to investigating general cases of polypharmacy, we will also investigate cases of inappropriate polypharmacy, which we define as individuals who are taking five or more drugs a day and who also have at least one criterion for increased drug risk. We reason that our findings may be valuable for public health decision-makers in Sao Paulo who face the progressively larger needs from a growing older population in use of polypharmacy.

4.2 AIMS

This study aims to, first, describe temporal trends and geographic variation in polypharmacy and inappropriate polypharmacy among the older adult population from Sao Paulo, Brazil.

We aim to identify individual factors associated with higher likelihood of polypharmacy, and to identify community factors associated with higher likelihood of polypharmacy when controlling for individual characteristics. We aim to use the same framework to investigate associations with inappropriate polypharmacy.

In the current article we address the individual and community-level characteristics associated with polypharmacy and inappropriate polypharmacy. We address the association between polypharmacy and multiple health system characteristics in Chapter 5.

4.3 METHODS

4.3.1 Data

The SABE Survey - Survey on Health, Well-Being and Aging

We use information from a household survey of non-institutionalized older adults living in Sao Paulo – the SABE Study (Survey on Health, Well-Being and Aging, or *Saúde, Bem-Estar e Envelhecimento* in the original in Portuguese). This survey sampled individuals 60 years and older in large metropolitan cities of Latin America in 2000. The study centers at the time were: Brazil (Sao Paulo), Argentina (Buenos Aires), Chile (Santiago), Uruguay (Montevideo), Mexico (Mexico City), Cuba (Havana) and Barbados (Bridgetown). In Brazil, the local team of investigators replicated the sample using the same questionnaire and methodology in 2006 and 2010.

The sampling process of the SABE survey in Brazil was conducted in two stages. In the first stage, census sectors (primary sampling units) were selected from the master sampling frame of the Brazilian 1996 Census. The census sectors were stratified according to the proportion of the heads of households who were illiterate, and were selected within each stratum with probability proportional to their size (number of households). In the second stage, households were selected within each census sector. In this stage all households had equal probability of selection. All persons over 60 years of age living in the household were selected to participate. In addition, individuals above 75 years of age were oversampled. These individuals were part of an additional sample, selected with equal probability for all subjects. The SABE study sample is representative of the non-institutionalized population aged 60 years and older from the metropolitan area of Sao Paulo when weighted according to the selection probability (Lebrao & Duarte, 2003; Alberto Palloni & Peláez, 2000). A detailed description of the survey, its participants, and main variables collected, is provided in Chapter 2.

The SABE sample comprehended a total of 2,143 participants in the first wave (2000), 1,413 participants in the second wave (2006) and 1,333 participants in the third wave (2010) (Box 4.1).

Box 4.1 The Sao Paulo SABE Study – Overview

Population	Years	Geographic Areas	Participants (N)	Data Collected
≥ 60 years old, non-institutionalized	2000, 2006, 2010	30 Sub-prefectures City of Sao Paulo	2143 (2000) 1413 (2006) 1333 (2010)	Socio-demographic Healthcare utilization Health Conditions Medication Use

Source: adapted from Lebrão, 2003, and the SABE dataset.

The SABE study collected extensive information on participants' demographic, socio-economic, and clinic characteristics. The survey recorded all drugs in use by the participants, including prescription and over-the-counter drugs, herbal and homeopathic products, and compounded substances. Participants self-reported drugs in use and investigators double-checked medicine cabinets, prescriptions and pill boxes. Drug information was recorded using alphanumeric codes developed by the World Health Organization's Anatomical Therapeutic Chemical classification (WHO-ATC) (WHO Collaborating Centre for Drug Statistics Methodology). There was no information on drug dosage or treatment duration.

We used the information on drug use to generate two variables: polypharmacy, which we defined as the use of five or more drugs per day, and inappropriate polypharmacy, which we described as the use of five or more drugs per day together with a drug risk criterion. We implemented three tools to assess drug risk in the SABE sample: the Beers Criteria, to capture potentially inappropriate prescribing (American Geriatrics Society Beers Criteria Update Expert, 2012), the ARS scale, to capture anticholinergic adverse effects (Rudolph et al., 2008), and the Hines list to capture clinically relevant drug-drug interactions (DDIs) (Hines & Murphy, 2011). A detailed description of each tool, as well as the methodology that we used for their implementation, is provided in Chapter 3.

We took advantage of the extensive clinical, demographic and health utilization characteristics collected in the SABE study to investigate multiple factors associated with polypharmacy at the individual level. We also aggregated some of the characteristics at the area level, in order to examine the possibility of contextual effects. The main variables utilized in this study, together with their description and the number of subjects with information, are provided in Table 4.1 below. The maximum number of subjects with information corresponds to the total of interviews across the three waves of the SABE study (N=4889).

Table 4.1 Individual characteristics collected by the SABE study

Variable	Type	N	Definition
Drug Utilization			
Medicines	count	4889	Number of prescriptions and over-the-count drugs in use. Medicines were coded using the WHO-ATC classification
Polypharmacy	binary	4889	Five or more prescription or over-the-counter drugs per day. Reference: zero to 4 drugs.
Inappropriate Polypharmacy	binary	4889	Five or more prescription or over-the-counter drugs per day, with at least one positive drug risk criterion[15]. Reference: any number of drugs with no risk criterion.
Excessive Polypharmacy	binary	4889	Ten or more prescription or over-the-counter drugs per day. Reference: zero to 4 drugs.
Socio-Demographic			
Age	count	4889	In years
Gender	binary	4889	Reference: males
Marital status	binary	4870	Married or in a civil union; reference: single, widowed or divorced
Income	continuous	4258	In Brazilian Reais (R$). Income from multiple sources (pensions, investments, wages, and others) was recorded. Per capita income was calculated by dividing the total reported income by the number of people that depended on the income as informed by the participants.
Health Insurance	binary	4886	Having private health insurance; reference: not having
Health Status			
Chronic Diseases	count	4889	Self-reported information on ever having been diagnosed by a doctor or nurse with one or more of the following conditions: hypertension, diabetes, heart disease, lung disease, stroke, cancer, psychiatric conditions, joint diseases, or osteoporosis.
Level of symptoms	count	4887	Self-reported information on having experienced persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo, tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence in the last 12 months.
Level of disability	count	4888	Self-reported information on having difficulty performing one or more activities of daily living: walking across a room, getting dressed, bathing, feeding, transferring to/from bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores.
Health Utilization			
Medical visits	count	4484	Self-reported information of the number of medical visits in the last 12 months.

[15] Drug Risk Criteria: Beers Criteria, Anticholinergic Risk Scale, and Hines list of Drug-Drug-Interactions (see detailed definitions in Chapter III).

Preventative exam	binary	4609	Self-reported information on having undergone a preventative exam in the last 24 months. Mammogram for women or prostate exam for men. Reference group: no preventative exam.
Behaviors			
Smoking	binary	4887	Reference: not currently smoking
Alcohol	binary	4884	Reference: no current use of alcohol

Source: SABE Study.

Demographic characteristics collected included age, gender, marital status (binary coded as married or in a civil union versus single, widowed or divorced), race (binary coded as white versus other), and religion (binary coded as catholic versus other). Socio-economic characteristics included years of schooling (number of school years completed; repeated grades were not considered), number of people who lived in the household, having children who were still alive (yes, no), having a caregiver (yes, no), and per capita income. Income was measured in Brazilian Reais. Participants were asked to inform their total income per month from all different sources (wages, investments, pensions, rent, remittances, etc.). Per capita monthly income was calculated by dividing the total reported income by the number of people that depended on the income as informed by the participants.

Health care utilization characteristics included health insurance coverage status (having or not having private health insurance), number of physician visits in the last 12 months, and whether the participant underwent a preventative exam (mammogram for women and prostate exam for men) in the last 24 months. Health status characteristics included presence and type of chronic conditions, presence and type of symptoms, level of disability, and self-reported health status. Information on chronic disease was obtained by asking participants if they were ever diagnosed by a doctor or nurse with one or more of the following conditions: hypertension, diabetes, heart disease, lung disease, stroke, neuropsychiatric disorders, cancer, osteoporosis, and arthritis. Positive responses were aggregated to obtain the number of chronic diseases reported by each participant.

Information on symptoms was obtained by asking participants whether they experienced any of the following symptoms in the last 12 months: persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo, tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence. Positive responses were aggregated to obtain the number of symptoms reported by each participant.

Information on disability was obtained by asking participants whether they had difficulties performing one or more activities of daily living: walking across a room, getting dressed, bathing, feeding, transferring to/from

bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores. Positive responses were aggregated to obtain the level of disability reported by each participant.

Self-reported health status was obtained by asking participants how they assessed their current health. Participants could choose from the following options: excellent, very good, good, regular, bad, or very bad health. The information provided by the participants was aggregated to create a binary variable "good" (excellent, very good, or good) versus "bad" (regular, bad or very bad) health status.

Health behavior characteristics included smoking, alcohol, and self-medication habits. Smoking was classified as currently smoking versus not currently smoking. Alcohol use was classified as current alcohol use versus no current alcohol use. Self-medication information was obtained by asking who had issued the prescription for each of the drugs that a participant was using. If any of the drugs been started by the participant on their own will, or on recommendation from family members/ friends, without a prescription issued by a health provider, the information was recorded as self-medication. If all drugs were prescribed by a health professional, or if the person did not take any drugs, the information was recorded as no self-medication.

Missing values were not a major problem in the SABE study. The characteristic with the most missing values was income, with 13% (n=631) missing values. The number of medical visits in the last 12 months was the second most frequently missing variable, with about 8% (n=406) of missingness. Having a preventative exam was the third with about 6% of missing values (n=280). All other variables had less than 5% missing values.

In our analysis, we excluded individuals with missing information for any variable, except for the three variables with most missing values that we described above (income, medical visits in the last 12 months, and preventative care in the last 24 months). The total number of individuals excluded from the analysis was 17 (0.8%) in 2000, 63 (4.5%) in 2006, and 24 (1.8%) in 2010.We dealt with missing values differently for each of these three variables.

For individuals with missing income information (n=631; 13%) we imputed the average per capita income for the corresponding gender and year. We identified individuals with imputed values by an indicator variable that

represented missing income. No association between polypharmacy and missing income was found across the multiple analyses.

There were 348 individuals with missing values for medical visits in the last 12 months in 2000 (representing 16% of the 2000 sample). These individuals were identified by an indicator variable for missingness and were included in the analyses for the year 2000. Missingness was associated with 64% lower odds of polypharmacy ($p<0.05$) in that year. We discuss this finding in chapter 4. Individuals with missing values for medical visits in the last 12 months in 2006 (N=54, 3.8% of the 2006 sample) and 2010 (N=4, 0.3% of the 2000 sample) were not included in the regressions.

There were 263 individuals (representing 19.7% of the 2010 sample) with missing values for preventative care in the last 24 months in 2010. These individuals were identified by an indicator variable for missingness and were included in the analyses for the year 2010. There was no association between missing information on preventative care in the last 24 months and the odds of polypharmacy in 2010. Individuals with missing values in 2000 (N=14, 0.65% of the 2000 sample) and 2006 (N=3, 0.21% of the 2006 sample) were not included in the regressions.

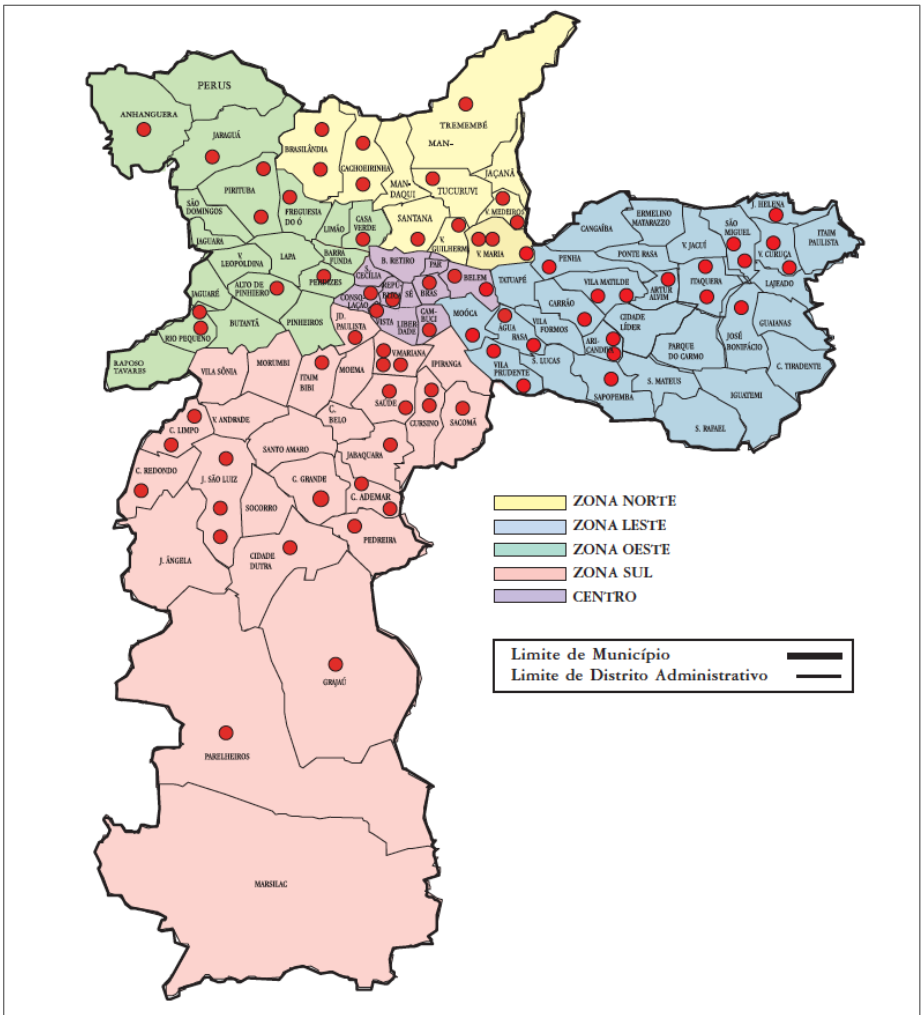
Geographic- Level Data

We took advantage of the distribution of SABE survey participants across the multiple areas of Sao Paulo (Figure 4.1) to implement a multi-level analysis investigating for community-level factors while controlling for the individual-level characteristics that we described above.

Most of the 31 geographic areas were represented in the SABE sample: 27 of the 31 sub-prefectures were represented in 2000; 30 sub-prefectures were represented in 2006; and 30 sub-prefectures were represented in 2010. The three sub-prefectures that were not represented in 2000 but were represented in 2006 and 2010 were: Ermelino Mattarazzo, Guaianases and Sao Mateus. The sub-prefecture that was not represented in any of the survey waves was Cidade Tiradentes. Because our study depended on characteristics measured at the individual

level, areas that had no participants could not be included in our analyses. The three areas that were not available in 2000 contributed information to the 2006 and 2010 analyses.

Figure 4.1 Distribution of survey participants across the geographic areas of Sao Paulo



Source: Lebrão, 2003.

Community Characteristics Calculated from the SABE Study Data

We calculated community-level characteristics using aggregated information from SABE study participants (Table 4.2). The participant-derived community characteristics were obtained for each sub-prefecture. Each characteristic was calculated as a weighted average of the participants living in that area. Importantly, each characteristic reflects the average of the characteristic only among older adults age 60 and over, and not the general population of each area.

Table 4.2 Community-Level characteristics derived from the SABE Study data

Variable	Definition
Drug Utilization	
Polypharmacy	% of individuals who were with polypharmacy
Socio-Demographic	
Age	Average age of the population in years
Gender	% of population who are females
Marital status	% of population who were married or in a civil union
Income	Average income in Brazilian Reais (R$)
Health Insurance	% of population with private health insurance
Health Status	
Chronic Diseases	Average number of chronic conditions per capita (conditions: hypertension, diabetes, heart disease, lung disease, stroke, cancer, psychiatric conditions, joint diseases, or osteoporosis)
Level of symptoms	Average number of clinical symptoms per capita (symptoms: persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo, tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence in the last 12 months)
Level of disability	Average level of disability per capita (activities: walking across a room, getting dressed, bathing, feeding, transferring to/from bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores)
Health Utilization	
Medical visits	Average number of medical visits in the last 12 moths per capita
Preventative exam	% of the population who underwent a preventative exam in the last 24 months (women: mammogram; men: prostate exam).
Behaviors	
Smoking	% of population currently smoking
Alcohol	% of population currently using alcohol

Note: Aggregated data from individuals 60 years old and over. Source: SABE database.

Community Characteristics Obtained from Official Government Sources

In order to compare the results from our sample-generated community variables, we utilized community variables obtained from official government sources. Specifically, we utilized the following variables:

- Percentage of seniors: proportion of residents age 60 years old and over. Data for 2000 and 2010 was obtained from the Brazilian Demographic Census; values for 2006 were calculated from Census data, assuming stable rates of increase during the time period.

- Rural area indicator: data for 2000 and 2010 was obtained from the Brazilian Demographic Census. We assigned a value of 1 if a sub-prefecture had 50% of more area with any rural characteristics. We assigned values for 2006 by interpolating information from the 2000 and 2010 Census, as follows: if a sub-prefecture had the same profile (rural-rural or urban-urban) in both years, we maintained the same value for 2006. Only three sub-prefectures had differing values between 2000 and 2010. All three sub-prefectures had rural characteristics in 2000 and did not have in 2010. In these three cases we assumed that there were no rural characteristics in 2006.

- All-cause mortality among individuals age 60 years old and over: data for all three years was collected from information from the Ministry of Health's Vital Statistics Registry, accessed via the Infocidade online database (http://infocidade.prefeitura.sp.gov.br/) in May, 2015.

- Hospital admissions, individuals age 60 years old and over: information obtained from the Sao Paulo City Health Secretariat online database, accessed May 2015 (http://www.prefeitura.sp.gov.br/cidade/secretarias/saude/tabnet/).

Conceptual Framework

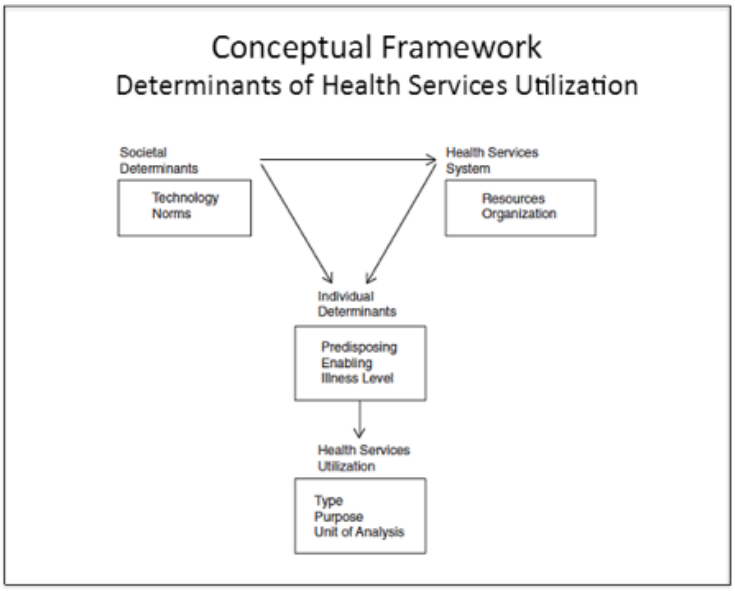
We draw from the conceptual framework of Societal and Individual Determinants of Medical Care Utilization developed by Andersen & Newman (R. Andersen & Newman, 1973) (Figure 4.2). In our study the main outcome of interest – "health service utilization" – is the use of polypharmacy; also, we study the occurrence of inappropriate polypharmacy.

Andersen and Newman's framework envisioned health services utilization as the result of a "sequence of conditions". At the individual level, the framework divided these conditions as: predisposing conditions ("the predisposition of the individual to use services"), enabling conditions (the individual's "ability to secure services"), and illness level (the diagnoses, level of symptoms and disability perceived by the individual or ascertained by the health provider).

At a broader level the framework identified determinants of health services use at the societal and health system's levels. The model assumes, however, that societal and health systems determinants affected service utilization only via modifications on individual-level determinants. The possibility that societal and health systems factors might directly affect health services utilization is not included in the model.

There are many alternative versions of the model, adapted to accommodate different levels of detail as well as different interconnections between the spheres of determinants. Of interest, one of the model's versions included a set of community determinants also affecting health services utilization (R. M. Andersen, 1995).

Figure 4.2 Conceptual framework – societal and individual determinants of medical care utilization



Source: Andersen & Newman (1973)

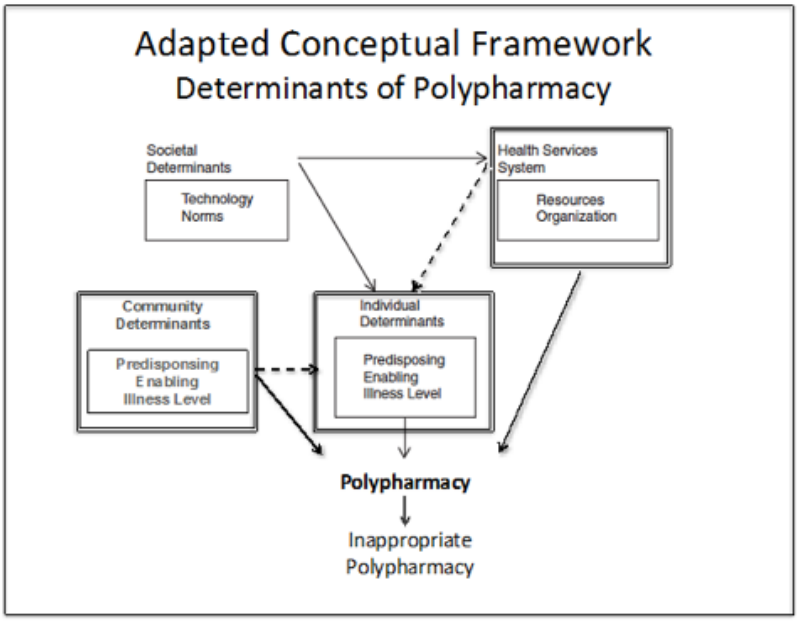
In this study, we begin with the conceptual model developed by Andersen, but adapt its graphic display to show the community determinants (Figure 4.2). We adapt it to identify this study's objectives, as we describe below (Figure 4.3):

We are interested in, first, estimating the effect of individual determinants with polypharmacy (straight arrow). Second, we are interested in estimating the effect of community determinants with polypharmacy. We assume that community determinants have both direct effects with polypharmacy (straight arrow) as well as indirect effects that act through modifications on individual conditions (dashed arrow). Lastly, we are interested in

estimating the direct effect of health system determinants with polypharmacy. In the present study, we assume that the effect of health services system determinants is captured by health services utilization. We will examine the effect of each of the health systems characteristics in the next chapter (Chapter 5).

We assume that societal determinants (technology and norms) are constant across areas. Technology represents drugs - the drugs available in the private market, the drugs included in government formularies – as well as their prices. Norms represent legislation and regulation establishing the rules for drug prescription, distribution and commercialization. Because our sample comes from one single city, it is highly unlikely that technology and norms would vary significantly across the different areas. For the most part drug regulation and legislation are established at the national level in Brazil. Only certain governmental formularies might be defined by states and cities; still, the formularies would be the same across all sub-prefectures. Still, it would be possible that stock-outs of government formulary drugs might affect some areas more than others. This might occur because of difficulties in transportation, logistics, or because of differences in administrative capacity in each of the areas. We cannot examine this possibility, however. We assume that the effect of area-level income may capture this effect if it is true.

Figure 4.3 Adapted conceptual framework used in this paper



Source: adapted from Andersen & Newman (1973), based on Andersen (1994).

Analytical Approach

Using figure 4.3 as the paradigm, we implement a series of analytical models in order to, first, estimate the relationships between individual-level determinants and polypharmacy; second, estimate the relationships between community-level determinants and polypharmacy; third, estimate the relationships between community-level determinants and polypharmacy while controlling for individual-level determinants.

Analytical Models

We model the log odds of polypharmacy using a logistic model [1] and a multi-level generalized latent mixed model [2], as follows:

$$Log\ [Pr(Y_{ij}=1)/\ Pr(Y_{ij}=0)] = \beta_0 + \beta_1 Individual_{ij} + \beta_2 Community_i \quad [1]$$

$$Log\ [Pr(Y_{ij}=1)/\ Pr(Y_{ij}=0)] = \beta_{0i} + \beta_1 Individual_{ij} + \beta_2 Community_i \quad [2]$$

Where:

- $Log\ [Pr(Y_{ij}=1)/\ Pr(Y_{ij}=0)]$ is the log odds of polypharmacy for subject *j* living in area *i*;
- β_0 represents the average baseline propensity for polypharmacy in the logistic model [1];
- $\beta_{0i,}$ which can be decomposed as $\beta_{0i} = \beta_0 + b_{0i}$, is a random intercept that represents the baseline propensity for polypharmacy in each geographic area in the multi-level model [2];
- $Individual_{ij}$ is the vector of predisposing, enabling, and illness level characteristics of subject *j* living in area *i;*
- $Community_i$ is a vector enabling and illness level characteristics of area *i*;
- $\beta_{1,}\ \beta_2$ and β_3 represent log odds ratios for a change in the response variable associated with a 1-unit change in each covariate, holding all others constant; we assume these relationships are constant across areas.

Assumptions

The following assumptions are common to both analytical models:

A) Underlying latent variable response:

$Y^*_{ij} > 0 \quad \rightarrow \quad Y_{ij} = 1$

$Y^*_{ij} <= 0 \quad \rightarrow \quad Y_{ij} = 0$

The models assume that there is a latent (unobserved) continuous response that represents the probability of the observed outcome (polypharmacy or no polypharmacy) for each subject *j* living in area *i*. A positive outcome (polypharmacy) will be observed when the individual's underlying latent variable Y^*_{ij} is greater than zero and a negative outcome (no polypharmacy) will be observed when the individual's underlying latent variable Y^*_{ij} is equal to or lower than zero.

B) Error term:

$E[\varepsilon_{ij} | Individual_{ij}, Community_i] = 0$

$\varepsilon_{ij} \sim logistic(0, \pi^2/3)$

ε_{ij} is an unobserved error term that represents the degree of heterogeneity in the propensity of polypharmacy (represented by the latent variable *Y*ij*) across all individuals. The models assume that the unobserved error term ε_{ij} has a logistic cumulative density function given all the covariates, with average of zero and variance equal to $\pi^2/3$.

C) The models assume that each covariate (represented by the vectors *Individual and Community*) has the same, fixed effect for every individual. However, the logistic models assume that the effect is the same for every individual regardless of the area where they live, but the multi-level model assumes that the fixed effect is conditional on the area where each individual lives (see G for more details on this assumption).

The following are additional assumptions specific to the multi-level model [2]:

D) Random intercept:

$E[b_{0i}] = 0$

$b_{0i} \sim N(0, \tau^2)$

The multi-level model [2] assumes that the baseline propensity for a positive outcome (polypharmacy) varies across areas. The baseline propensity of each individual area is captured by its random intercept b_{0i}. Differences in the area-specific baseline propensity for polypharmacy are a result of differences in both measured and unmeasured characteristics of each area. The multi-level model assumes that the random intercepts b_{0i} have a normal distribution independent from the area-level covariates, with mean of zero and variance denoted by τ^2.

E) Correlation between individuals living in the same geographic area:

$\text{Corr}(Yij, Yik) = \rho$

The multi-level model assumes that the propensity for polypharmacy for individuals *j* and *k* living in the same geographic area is correlated. The model assumes that responses are independent once the baseline propensity for polypharmacy of an area (captured by the area-specific random intercept b_{0i}) is accounted for.

F) *Total* variance of the response variable:

$Var(Y^*ij) = \text{Var}(\varepsilon_{ij}) + \text{Var}(b_{0i})$

Different from the logistic model, the multi-level model assumes that the total variance in the propensity for polypharmacy (represented by the latent variable *Y*ij*) across all individuals equals the variance of the error term plus the variance of the random intercept.

G) Conditional vs. marginal effects: while the coefficients from the logistic model [1] represent average effects at the population level, the coefficients from the multi-level model [2] represent effects within a given geographic area. In the multi-level model there is a different baseline propensity for polypharmacy in each geographic area. This baseline propensity must be taken into consideration when interpreting the fixed effects from the various covariates in the multi-level model. In the multi-level model a coefficient represents the expected change in the log odds of polypharmacy associated with a one-unit change in a given covariate (holding all other covariates constant) for an individual living in an average area.

Implementation

We ran a series of descriptive statistics in order to describe the levels of individual and geographic characteristics at all survey waves. The individual characteristics were explored using inverse probability weighting in order to reconstruct the non-institutionalized population of 60 year-olds and over in Sao Paulo. The geographic characteristics were explored using one data point per each geographic area. The descriptive analysis of the geographic characteristics was performed without the use of weights.

For the analysis of the associations between the multiple individual and geographic characteristics and the outcome of interest (polypharmacy) we implemented the logistic and multi-level approaches described above. We implemented the logistics models that do not account for geographic clustering because these are frequently used in the literature. We compared the logistic model results to multi-level models accounting for geographic clustering, in order to understand the extent to which ignoring the geographic clustering may impact findings in this context.

We implemented three different versions of each model: *Individual Models* (Model 1) using only individual-level covariates, *Geographic Models* using only area-level covariates, and *Full Models* (Model 2) using both individual and area-level covariates.

We ran the analytical models separately for each year that the survey was available (2000, 2006 and 2010). Following the sample design, we applied inverse-probability weights to all models in order to reconstruct the population of non-institutionalized individuals 60 year-old and over living in Sao Paulo in each year. In addition to individual weights, the multi-level model also required the specification of area-level weights. Because the area-level weights had been factored in the calculation of individual weights at the time of survey design, we assumed that all areas had equal weights and we set all area-level weights equal to 1. In order to account for unequal variances we utilized robust standard errors clustered at the primary sampling units (census tracts) in the logistic models. The use of weights automatically provides robust standard errors in the multi-level models.

In addition, we ran a series of model checks and sensitivity analyses in order to assess the fit of our chosen models and the robustness of our findings.

4.4 RESULTS

4.4.1 Part 1 - Descriptive Analysis

Sample Characteristics – Overview

The final sample of the SABE survey constituted of 2,143 individuals living in 27 areas in 2000; 1,413 individuals living in 30 areas in 2006; and 1,333 individuals living in 30 areas in 2010 (Table 4.3).

Individuals did not necessarily participate in all three waves. Of the total 4,889 observations across the three survey waves, 2,796 (57%) were individuals who participated in only one wave; 1,408 (29%) participated in two survey waves; and 685 (14%) participated in three survey waves. Because the majority of participants had contributed information to a single survey wave, and because those that contributed with two waves of data were distributed across the survey waves (i.e, were not all concentrated in the same two waves), we utilized information from all participants who had available data in each year.

In 2000, an average of 107.7 participants were included per sub-prefecture (ranging from 13 to 182 per sub-prefecture). There was a tendency of decreasing sample size per area, so that in 2006 the average number of participants per area was 63.8 (ranging from 5 to 111) and in 2010 the average number of participants per area was 63.8 (ranging from 4 to 105).

Table 4.3 Overview of the SABE survey

	2000	2006	2010
Nr. of Areas	27	30	30
Nr. participants	2,143	1,413	1,133
Participants per Area			
Avg (sd)	107.7 (48.5)	63.8 (26.2)	56.8 (21.7)
Min–max	13–182	5–111	4–105

Polypharmacy and Drug Utilization

Use of medicines among the population 60 years and older increased significantly between 2000 and 2010. The number of people taking drugs increased as well as the number of medications per person. The prevalence of polypharmacy increased significantly in the 10-year period. Table 4 summarizes the drug utilization metrics in each of the survey years.

The prevalence of taking at least one drug among the population of 60 year-olds and over was estimated to be 84.3% in 2000 (95% CI: 82.5% - 86.2%). In 2010, this prevalence was 90.6% (95% CI: 88.9% - 92.4 The maximum number of drugs per day that any individual in the sample took was 14 in 2000, 15 in 2006, and 17 in 2010.

The estimated prevalence of polypharmacy (five or more drugs) was 16.1% in 2000 (95% CI: 14.4% - 17.9%). The prevalence of polypharmacy more than doubled in 2010, up to a total of 37.6% (95% CI: 34.8 – 40.4%). Women had higher prevalence of polypharmacy both at baseline and after 10 years (2000 prevalence= 19.9%, 95% CI: 17.5% - 22.3%. 2010 prevalence= 42.7%, 95% CI: 39.1% - 46.3%). Men had lower prevalence of polypharmacy at baseline (2000 prevalence=10.7%, 95% CI: 8.3% - 13.1%) and also after 10 years (2010 prevalence= 30% 95% CI: 25.5% 34.6%). The rate of increase in polypharmacy was higher in men than women - almost three-fold increase compared to a doubling.

The prevalence of inappropriate polypharmacy (five or more drugs where at least one is identified as inappropriate by the Beers Criteria, the anticholinergic risk scale or the Hines list of clinically relevant drug-drug interactions) was 12.6% in 2000 (95% CI: 11.0% - 14.1%). It almost doubled in the 10-year interval, to 22.5% (95% CI: 20.1% - 24.9%). However, the proportion of the population with inappropriate polypharmacy declined. In 2000, an estimated 78% of individuals with polypharmacy had inappropriate polypharmacy; in 2010, this proportion was 60%.

The prevalence of excessive polypharmacy (ten or more drugs) was estimated in 0.7% in 2000 (95% CI: 3.4% - 1.2%) and 4.5% in 2010 (95% CI: 3.3% - 5.7%), a six-fold increase. The rate of increase of excessive

polypharmacy far outweighed the rate of increase of all other drug utilization metrics, including any medication use, number of drugs per person, polypharmacy, and inappropriate polypharmacy (Table 4.4).

Table 4.4 Polypharmacy and drug utilization across the survey waves

Year Weighted mean(sd)*	2000 N=2143	2006 N=1413	2010 N=1333	st.diff** 2010-2000
% Taking at least 1 medicine	84.3 (36.3)	86.9 (33.7)	90.6 (29.1)	0.1
Avg. nr. of medicines	2.51 (2.15)	3.12 (2.42)	3.94 (2.94)	0.39
% Polypharmacy (a)	16.1 (36.8)	26.0 (43.9)	37.6 (48.5)	0.4
% Inappropriate polypharmacy (b)	12.6 (33.1)	17.1 (37.7)	22.5 (41.8)	0.2
% Excessive polypharmacy (c)	0.7 (8.6)	1.8 (13.3)	4.5 (20.7)	0.2

Notes: *Weighted averages and standard deviations calculated using inverse selection probability weights specific for each survey wave. Variables have no missingness except noted otherwise.

** St.diff: standardized difference between 2010 and 2000. Calculated as the difference in weighted means (mean 2010 - mean 2000) divided by a pooled standard deviation (square root of the sum of variance 2010 plus variance 2000).

(a) Polypharmacy: use of five or more drugs a day.

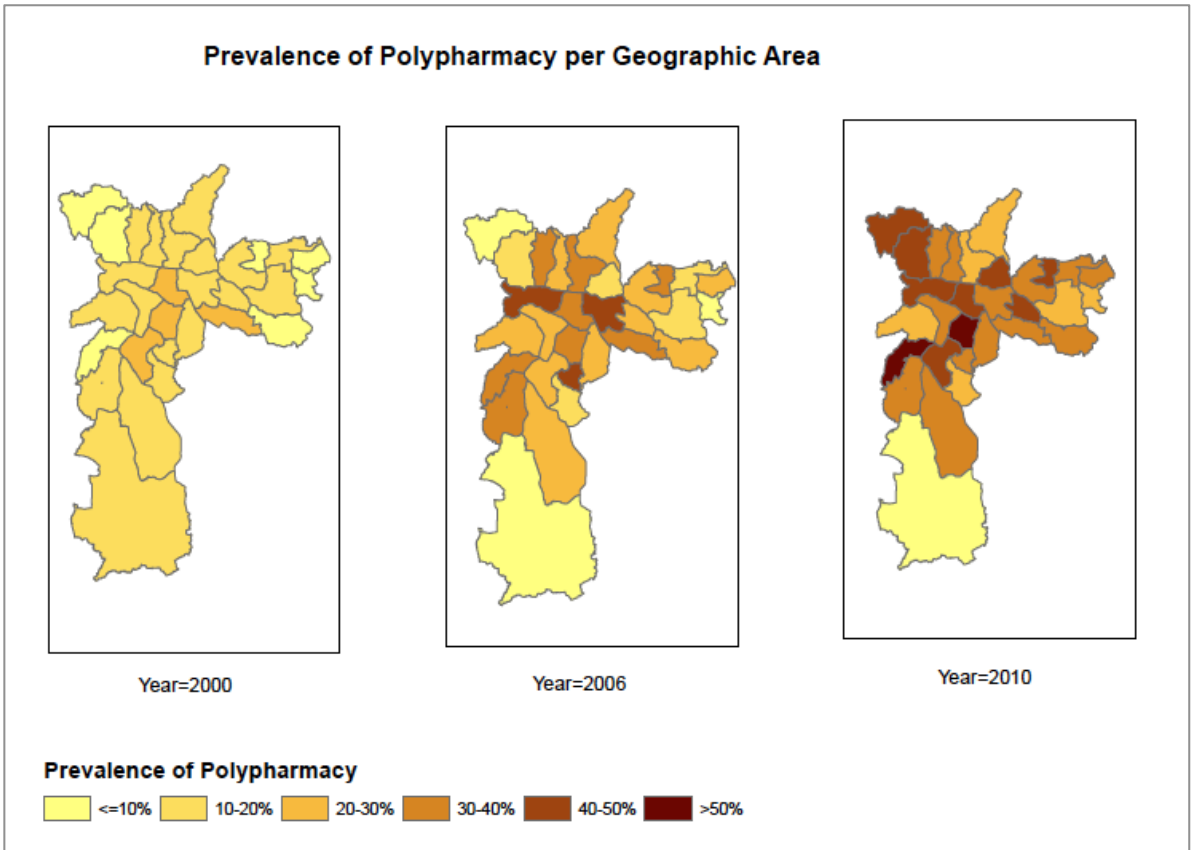
(b) Inappropriate polypharmacy: use of five or more drugs where at least one is identified as inappropriate by the Beers Criteria, the anticholinergic risk scale or the Hines list of clinically relevant drug-drug interactions.

(c) Excessive polypharmacy: use of ten or more drugs a day.

Geographic Variation in Polypharmacy

There was significant variation in the rates of polypharmacy and inappropriate polypharmacy across the multiple geographic areas of the city of Sao Paulo at each given year. Across time, areas tended to have greater prevalence of polypharmacy on average. Also, the variability in rates of polypharmacy across areas tended to increase. Figure 4.4 displays the evolution in the rates of polypharmacy across the multiple Sao Paulo sub-prefectures from 2000 to 2010.

Figure 4.4 Prevalence of polypharmacy among older adults across the Sao Paulo geographic areas, 2000-2010



Source: SABE dataset.

In 2000, the estimated average prevalence of polypharmacy among individuals 60 years old and older across the geographic areas was 15.1% (95% CI: 11.5%-18.7%). The lowest prevalence of polypharmacy in any given area was 1.3% and the highest was 25.1%. In 2010, the estimated average prevalence of polypharmacy was 36.9% (95% CI: 33.5%-40.3%). The lowest prevalence of polypharmacy in a geographic area was 6.6% and the highest was 56.6%.

The average prevalence of polypharmacy across the geographic areas grew 2.5 times from 2000 to 2010. Table 4.5 summarizes the trends in the rates of polypharmacy and inappropriate polypharmacy at the geographic area level for each of the survey years.

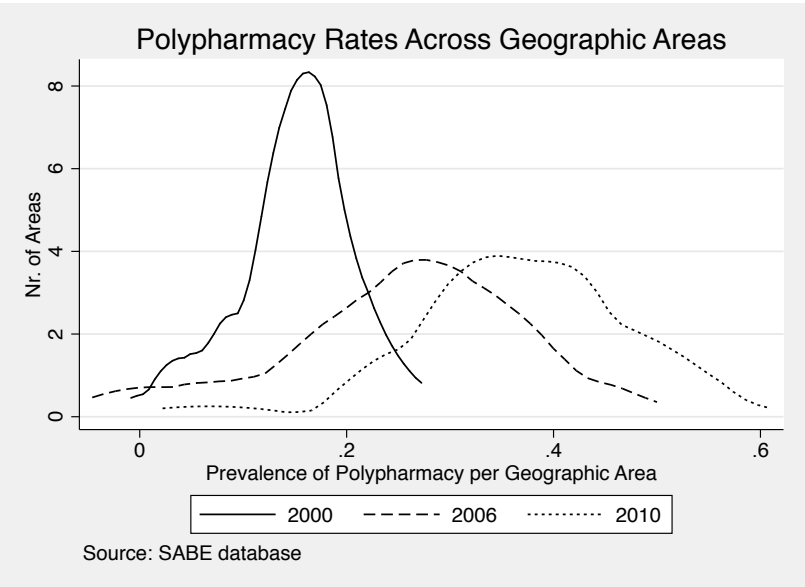
Table 4.5 Average Rates of Polypharmacy and Inappropriate Polypharmacy among 60 year-olds and Older across the Geographic Areas of Sao Paulo

		2000 N=27 areas	2006 N=30 areas	2010 N=30 areas
Polypharmacy	Mean(sd)	15.1% (5.4)	25.3% (11.3)	36.9% (10.0)
	Range	1.3–25.1%	0.0–45.4%	6.6–56.6%
Inappropriate Polypharmacy	Mean(sd)	11.9% (4.9)	16.1% (8.0)	22.1% (8.5)
	Range	0.0–20.2%	0.0–27.7%	0.0–40.9%

Notes: Means and standard deviations were calculated using one data point per area. Rates reflect estimated prevalence among individuals 60 years and older in each geographic area. Polypharmacy: use of five or more drugs a day. Inappropriate polypharmacy: use of five or more drugs per day, plus at least one positive measure of drug risk.

The distribution of polypharmacy rates across the geographic areas tended to be left-skewed in all years, representing the fact that, while most areas tended to have rates of polypharmacy closer to the average, there were some areas with lower rates (Figure 4.4). The spread of the distribution increased over time, reflecting higher variability in the prevalence of polypharmacy across geographic areas over time.

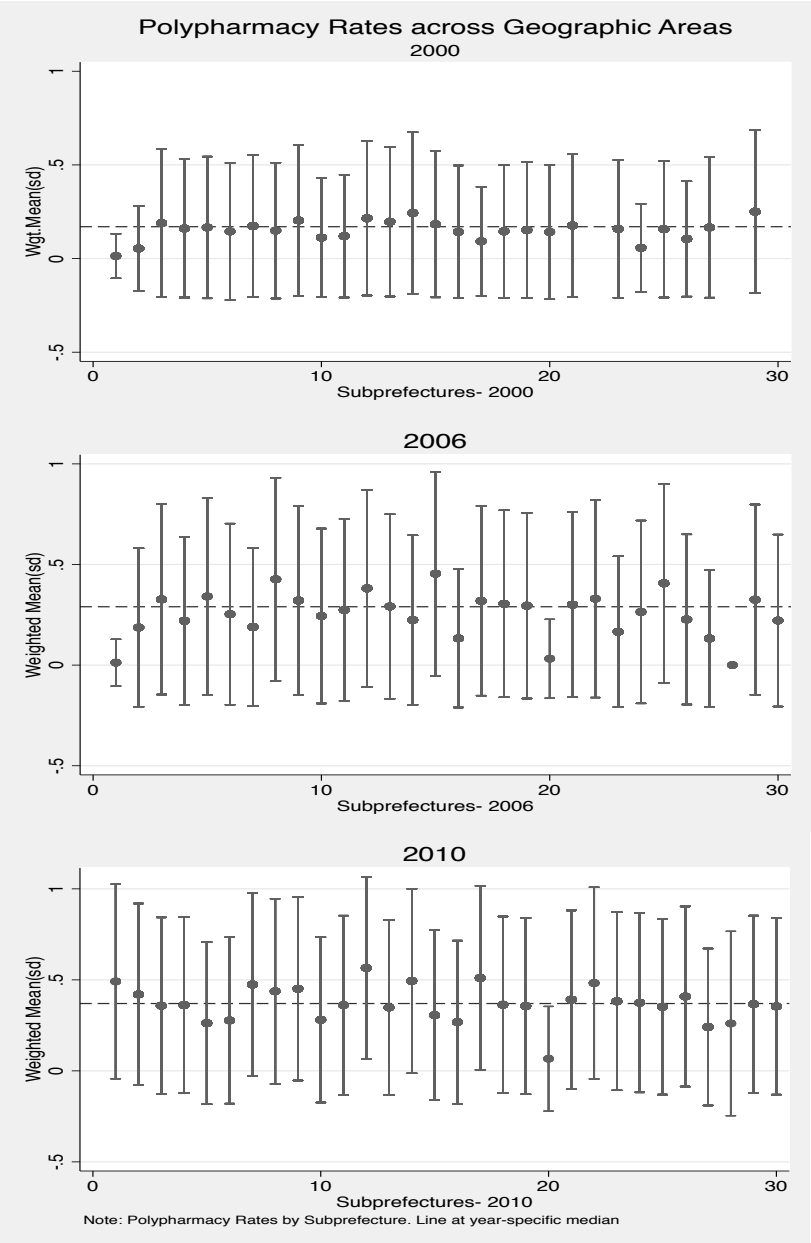
Figure 4.5 Trends in the Distribution of Polypharmacy Prevalence per Geographic Area over Time (Kernel Density Estimates)



Note: estimated prevalence of polypharmacy among 60 year-olds and over living in each sub-prefecture

Figure 4.6 displays means and standard deviations in the prevalence of polypharmacy per geographic area per year, and displays the median prevalence of polypharmacy across all areas for each year (dotted lines). The increase in average rates of polypharmacy and in the variation around overall common values can be visualized over time.

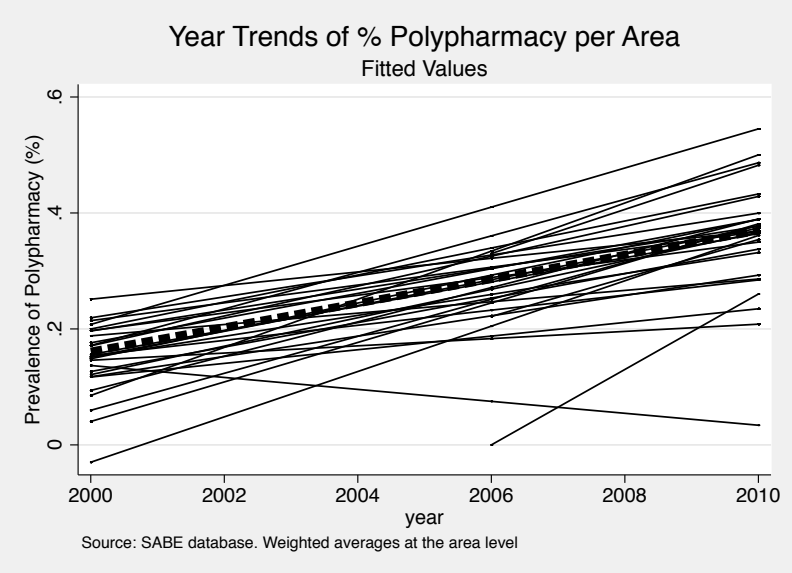
Figure 4.6 Average and Standard Deviations for the Prevalence of Polypharmacy in each of the Sao Paulo Sub-Prefectures, by Year



Note: Average ± standard deviations in the prevalence of polypharmacy among 60 year-olds and over presented for each of the Sao Paulo sub-prefectures. Source: SABE database.

Most sub-prefectures tended to experience increases in the prevalence of polypharmacy over time. However, trends were not uniform across areas. Figure 4.7 displays fitted lines identifying average trends per area over the 10-year interval.

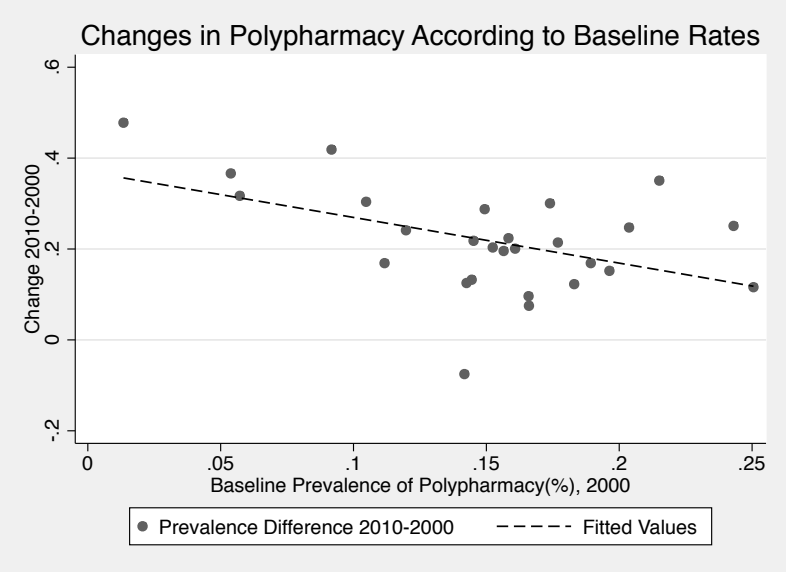
Figure 4.7 Trends in Polypharmacy Rates per Area over the 10-Year Interval



Note: Fitted lines demonstrate the average linear trajectory of the weighted rates of polypharmacy at the area level over time. Standard errors and confidence intervals not shown. One line per geographic area. Dotted line represents the overall average.

To understand the differences in the rates of change across areas we plotted the 10-year differences against the baseline prevalence of polypharmacy for each of the areas (Figure 4.8). The highest differences seemed to have occurred in areas with lower baseline prevalence of polypharmacy, possibly representing regression to the mean.

Figure 4.8 10-Year Differences in the Prevalence of Polypharmacy according to the Baseline Values



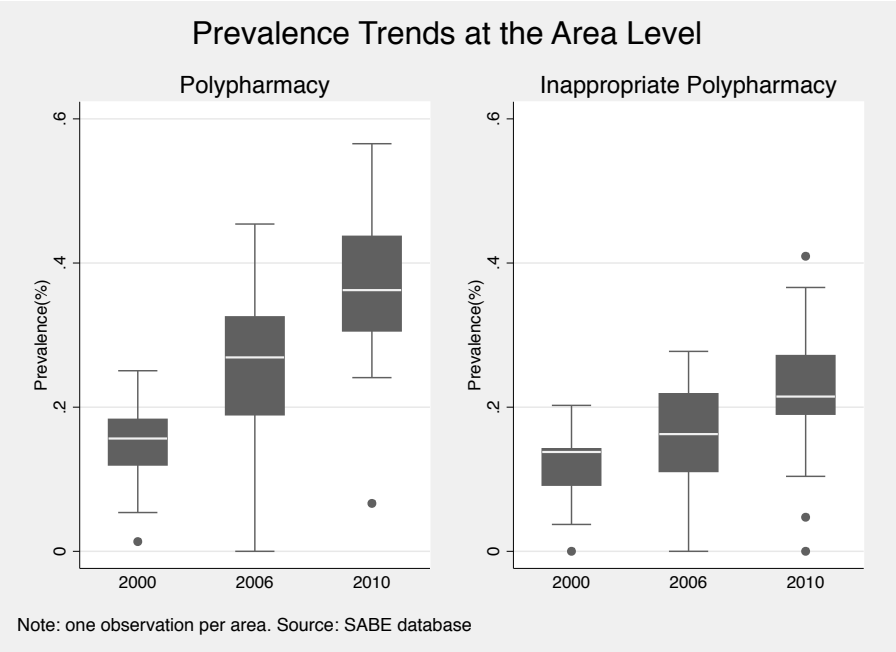
Note: One data point per geographic area. Source: SABE database.

Geographic Variation in Inappropriate Polypharmacy

The overall trends in the prevalence of inappropriate polypharmacy tended to follow those of polypharmacy across the geographic areas. There was a tendency of increase in average rates of inappropriate polypharmacy over time across most areas, and a tendency of increasing variation around common values. However, prevalence of inappropriate polypharmacy was lower than prevalence of polypharmacy (Figure 4.9).

In 2000 the estimated average prevalence of inappropriate polypharmacy among 60 year-olds and over across the geographic areas was 11.9% (95% CI: 9.1% - 14.7%). By 2010 the prevalence had almost doubled to 22.1% (95%CI: 19.4%-24.8%). There was a very high correlation between rates of polypharmacy and rates of inappropriate polypharmacy at baseline across the areas (r=0.89); this correlation was still positive but lower in magnitude in 2010 (r=0.55). The positive correlations between rates of polypharmacy and inappropriate polypharmacy indicate that, in general, areas with higher rates of polypharmacy tend to have higher rates of inappropriateness. However, this link tended to be weaker over time.

Figure 4.9 Trends in Prevalence of Polypharmacy and Inappropriate Polypharmacy across the Geographic Areas



Note: estimated prevalence among non-institutionalized individuals 60 years and older. Source: SABE database.

Individual Characteristics across the Survey Waves

SABE participants tended to be composed of older and sicker individuals, who sought more care (including preventative care), and had higher incomes and health insurance coverage over time. Table 4.6 summarizes the main individual characteristics in each of the survey waves. We present inverse-probability weighted averages, which reflect the characteristics of the Sao Paulo older adult population in each year.

The average age of individuals increased from 69.4 in 2000 to 70.4 years in 2010. The maximum age increased from 100 years in 2000 to 104 years in 2010. On average around 60% of the population was composed of women and 57% of individuals were married; these proportions did not significantly change over time. The prevalence of chronic diseases increased from 79% in 2000 to 86% in 2010, accompanied of an increase in the number of chronic diseases per person, from an average of 1.64 in 2000 to 2.13 in 2010. Individuals tended to report slightly higher number of symptoms (average of 1.47 symptoms per person in 2000 and 1.56 in 2010) and disability (average of difficulty in 1.23 activities of daily living in 2000 and 1.55 in 2010).

Individuals tended to have higher incomes and higher rates of private health insurance over time. The average per capita income almost tripled from R$ 370.80 in 2000 to R$ 905.01 in 2010. The maximum per capita income increased four fold from R$ 7,000.00 in 2000 to R$ 25,000.00 in 2010. These numbers are not adjusted for inflation. In 2000, 41% older adults had private health insurance, increasing moderately to 45% in 2010.

Individuals were more likely to seek care over the ten year period: an average of 77% of individuals reported seeking care at least once in the last 12 months in 2000, increasing to 87% in 2010. Those who sought care tended to have a similar distribution of number of visits in all years, with the majority reporting between 1-6 visits in the last 12 months (43% in 2000 and 72% in 2010) and a very low number of individuals reporting more than 24 visits in the last 12 months (1% in 2000 and 2% in 2010). The levels of preventative care, represented by mammograms in women or prostate exam for men in the last 24 months, increased from 40% in 2000 to 61% in 2010. Levels of smoking were low and tended to decrease over time (16% in 2000 and 12% in 2010), but levels of alcohol use were moderately high and tended to be stable over time (32% in 2000 and 2010).

Table 4.6 Individual Characteristics across the Survey Waves

Year Weighted mean(sd)*	2000 N=2143	2006 N=1413	2010 N=1333	st.diff 2010-2000**
Socio-Demographic				
Avg. age	69.4 (7.42)	69.6 (7.51)	70.4 (8.27)	0.09
% of subjects aged 60-69	0.59 (0.49)	0.59 (0.49)	0.54 (0.50)	-0.1
% of subjects aged 70-79	0.30 (0.46)	0.30 (0.46)	0.31 (0.46)	0.01
% of subjects aged 80-89	0.10 (0.29)	0.10 (0.29)	0.13 (0.34)	0.11
% of subjects aged 90+	0.01 (0.12)	0.02 (0.13)	0.02 (0.15)	0.06
Female gender	0.59 (0.49)	0.59 (0.49)	0.60 (0.49)	0.02
Married (a)	0.57 (0.50)	0.57 (0.49)	0.54 (0.50)	-0.03
Per Capita Income (b)	370.80 (560.3)	675.26 (1210.2)	905.01 (1611.2)	0.31
Private health Insurance (c)	0.41 (0.49)	0.44 (0.50)	0.45 (0.50)	0.05
Health Status				
% with chronic diseases (d)	0.79 (0.41)	0.86 (0.35)	0.86 (0.35)	0.14
Nr. Chronic Diseases (d)	1.64 (1.28)	2.09 (1.51)	2.13 (1.51)	0.25
Avg. nr. symptoms (e)	1.47 (1.63)	1.33 (1.57)	1.56 (1.67)	0.04
% no symptoms	0.37 (0.48)	0.39 (0.49)	0.35 (0.48)	-0.03
% mild	0.39 (0.49)	0.42 (0.49)	0.40 (0.49)	0.02
% moderate	0.21 (0.41)	0.16 (0.37)	0.21 (0.41)	0.00
% severe	0.03 (0.16)	0.03 (0.17)	0.03 (0.17)	0.03
Avg. level of disability (f)	1.23 (2.38)	1.61 (2.71)	1.55 (2.61)	0.09
% no disability	0.65 (0.48)	0.56 (0.50)	0.55 (0.50)	-0.13
% mild	0.26 (0.44)	0.30 (0.46)	0.32 (0.47)	0.10
% moderate-severe	0.10 (0.29)	0.14 (0.34)	0.13 (0.33)	0.07
Health Care Utilization				
% sought any care in last 12mo (g)	0.77 (0.42)	0.89 (0.31)	0.87 (0.34)	0.18
% Low utilization (g)	0.62 (0.48))	0.71 (0.46)	0.85 (0.36)	0.26
% High utilization (g)	0.21 (0.41)	0.29 (0.46)	0.15 (0.36)	-0.16
% preventative exam last 24mo (h)	0.40 (0.49)	0.56 (0.50)	0.61 (0.49)	0.50
Behaviors				
Current smoking (i)	0.16 (0.37)	0.14 (0.35)	0.12 (0.32)	-0.08
Current alcohol use (j)	0.32 (0.47)	0.31 (0.46)	0.32 (0.47)	0.00

Notes:

*Weighted averages and standard deviations calculated using inverse probability weights specific for each survey wave. Variables have no missingness except noted otherwise.

** St.diff: standardized difference between 2010 and 2000. Calculated as the difference in weighted means (mean 2010 - mean 2000) divided by a pooled standard deviation (square root of the sum of variance 2010 plus variance 2000).

(a) Married or in a civil union. Reference: single, widowed or divorced. Number of missing values: 1 (2000), 2 (2006) and 16 (2010).

(b) In Brazilian Reais. Number of missing values: 339 (2000), 171 (2006), 121 (2010).

(c) Number of missing values: 2 (2000), 1 (2006).

(d) Self-reported information on ever having been diagnosed by a doctor or nurse with one or more of the following: hypertension, diabetes, heart disease, lung disease, stroke, cancer, psychiatric conditions, joint diseases, or osteoporosis.

(e) Having experienced persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo, tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence in the last 12 months. Mild: 1-2 symptoms. Moderate: 3-5 symptoms. Severe: 6+ Symptoms. Number of missing values: 2 (2010).

(f) ADL: activities of daily living. Having difficulty performing one or more of the following activities: walking across a room, getting dressed, bathing, feeding, transferring to/from bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores. Mild: 1-4 ADLs. Moderate-Severe: 5+ ADLs. Maximum exhibited in the sample: 12 ADLs. Number of missing values: 1 (2000).

(g) Low utilization: up to 6 medical visits per year. High utilization: more than 6 medical visits per year (over 75th percentile). Number of missing values: 348 (2000), 54 (2006), 4 (2010).

(h) Mammogram for women or prostate exam for men. Number of missing values: 14 (2000), 3 (2006), 263 (2010).

(i) Reference: not currently smoking. Number of missing values: 1 (2000), 1 (2010).
(j) Reference: no current use of alcohol. Number of missing values: 4 (2006), 1 (2010).

Geographic Characteristics across the Survey Waves

The populations across the multiple geographic areas tended to be older and sicker, have higher incomes, higher health insurance coverage, and higher health care utilization over time. Table 4.7 summarizes the geographic area characteristics in each of the survey years. These characteristics were calculated from the survey data and they apply exclusively to the population of 60 year-olds and over in each area.

The average age of the population 60 years and over in each area increased from 69.33 years in 2000 to 70.55 years in 2010. The prevalence of chronic diseases in each area increased from 80% in 2000 to 86% in 2010, and the average number of chronic diseases in the population increased from an average of 1.65 per person in 2000 to 2.01 in 2010.

Average per capita incomes at the geographic area level increased almost three fold, from R$ 341.97 in 2000 to R$ 920.72 in 2010. In this period, the average rates of private insurance coverage among 60 year-olds and over increased from 37% to 44%, and health care utilization increased significantly by all metrics (more preventative exams, higher frequency of receiving any medical visits in the last 12 months, and higher percentage of high utilizers – having utilization above the median for the year). The characteristics calculated from the survey data were in line with information for each area collected from official sources such as the Brazilian census, the Brazilian public health system databases, and online databases maintained by the State and the City of Sao Paulo.

Table 4.7 Geographic characteristics across the survey waves

Year Mean(sd)*	2000 N=27 areas	2006 N=30 areas	2010 N=30 areas	st.diff 2010-2000**
Socio-Demographic* **				
Avg. age (years)	69.33 (1.83)	69.34 (3.77)	70.55 (3.73)	0.29
Avg. prevalence of NCDs (%) (a)	0.80 (0.06)	0.87 (0.08)	0.86 (0.05)	0.79
Avg. Nr. of NCDs per person (a)	1.65 (0.18)	1.95 (0.27)	2.01 (0.28)	1.09
Avg. per capita income (b)	341.97 (206.6)	654.60 (465.5)	920.72 (621.6)	0.88
% Private health insurance	0.37 (0.20)	0.42 (0.20)	0.44 (0.21)	0.22
Health Care Utilization* **				
% Preventative exams (c)	0.38 (0.11)	0.56 (0.10)	0.74 (0.08)	2.78
% Any care in last 12 mo. (d)	0.77 (0.08)	0.90 (0.11)	0.86 (0.10)	0.71
% High care utilizers (d)	0.21 (0.05)	0.29 (0.15)	0.15 (0.07)	-0.98

Notes:

* Means and standard deviations were calculated using one data point per area.

** Standardized differences between the 2010 and 2000 calculated as the difference in weighted means (mean 2010 - mean 2000) divided by a pooled standard deviation (square root of the sum of variance 2010 plus variance 2000). Standardized differences between 2010 and 2006 were presented when data for 2000 was not available.

*** Average age, number of chronic diseases, per capita income, health insurance, and preventative services utilization were calculated from the SABE survey data. All other variables were obtained from official public sources in Sao Paulo, Brazil. With exception of the percentage of seniors, all other variables refer to non-institutionalized individuals 60 years and older living in Sao Paulo.

**** Health care utilization rates are presented among individuals 60 years and older. All health resources are presented as number of resources per 100,000 population.

(a) NCDs: non-communicable diseases. Self-reported information on ever having been diagnosed by a doctor or nurse with one or more of the following conditions: hypertension, diabetes, heart disease, lung disease, stroke, cancer, psychiatric conditions, joint diseases, or osteoporosis.

(b) In Brazilian Reais.

(c) Mammogram (women) or prostate exam (men) in the last 24 months among individuals 60 years and older.

(d) Percentage of individuals 60 years and older who utilized more than six medical visits (75^{th} percentile) in the last 12 months.

4.4.2 Part 2 –Links between Polypharmacy and Individual Characteristics

Overall

We first investigate the links between polypharmacy and individual-level characteristics ignoring information about the area where individuals reside. We utilize logistic regression models to investigate these associations. We apply inverse probability weights to reconstruct the population of 60 year-olds and over living in the city of São Paulo at each year. We cluster the standard errors at the census tract level (primary sampling units) in order to account for unequal variances. Table 4.8 displays the results of weighted logistic regression models for the odds of polypharmacy using individual characteristics exclusively (*Individual Models*).

These models estimate that the baseline odds of polypharmacy for a 60-year-old individual who is male, not married, does not have health insurance and does not have an income, does not have any chronic diseases, any symptoms or disability, has not sought care in the last 12 months, did not undergo a preventative prostate exam in the last 24 months, and does not smoke or use alcohol, as 0.004 in 2000, 0.011 in 2006 and 0.013 in 2010. These values of odds allow us to calculate corresponding probabilities of polypharmacy of 0.4% in 2000, 1% in 2006 and 1.3% in 2010.

At the individual level, the most important factors associated with polypharmacy were those reflective of health status. The number of chronic diseases was the characteristic with the highest association with polypharmacy at all survey waves. The association between chronic diseases and polypharmacy was found to vary between women and men. With the exception of 2006, this difference was statistically significant, at the $p<0.05$ (2000) and $p<0.01$ (2010) levels.

For each additional 10 years of age, the odds of polypharmacy were increased by 32% in 2000, and 48% in 2010, all other things being equal. Both associations were statistically significant at the 0.01 level. Women had three times higher odds of polypharmacy than men in 2000 ($p<0.01$) and 2.14 times higher odds of polypharmacy than men in 2010 ($p<0.01$). When controlling for all other individual characteristics, marital status was not significantly associated with polypharmacy, although in 2006 there was a marginally significant relationship, indicating 40% higher odds of polypharmacy among married individuals as compared to not married.

For men, each additional chronic disease was associated with 2.2 times greater odds of polypharmacy in 2000 and 2006, and 3 times greater odds of polypharmacy in 2010 (all significant at the $p<0.01$ level), holding other characteristics constant. While women tended to have significantly higher odds of polypharmacy than men at baseline, the increase in the odds of polypharmacy associated with each additional chronic disease was slightly lower (28% in 2000 and 34% lower in 2010) among women than it was estimated among men.

To illustrate, while each additional chronic disease was associated with 2.2 times higher odds of polypharmacy among men in 2000, each additional chronic disease was associated with 1.64 times higher odds of

polypharmacy among women. In 2010, while each additional chronic disease was associated with three times higher odds of polypharmacy among men, each additional chronic disease was associated with two times higher odds of polypharmacy among women. There were no other differential effects between women and men that could be detected in our sample.

There was a dose-response relationship between higher levels of physical symptoms with higher odds of polypharmacy, when controlling for the same levels of chronic diseases, health care utilization, and all other individual characteristics. Level of clinical symptoms is utilized in this study as a metric of disease severity, as it helps differentiate between individual with controlled from those with non-controlled conditions. We assume that persons with a chronic disease that is under control will have fewer symptoms than a person with an actively symptomatic chronic condition.

The dose-response pattern was present in all years but was most striking in 2000, where a person with one or two symptoms had 2.3 times higher odds of polypharmacy, a person with three to five symptoms had 2.8 times higher odds of polypharmacy, and a person with six or more symptoms had seven times higher odds of polypharmacy when compared to individuals with no symptoms (and keeping all other characteristics constant).

In 2000, all these associations were statistically significant at the $p<0.01$ level. In 2006 and 2010 the dose-response pattern was still observed but the increases in magnitude associated with higher levels of symptoms were less striking than 2000. Also, only the highest level of symptoms was statistically significantly associated with polypharmacy in 2006 (and only at the $p<0.10$ level) and in 2010 (at the $p<0.01$ level). In 2010 the second-lowest level of symptoms was also associated with polypharmacy, at the $p<0.10$ level – holding all other factors constant, and when compared to individuals with no symptoms.

Higher levels of disability (as measured by the difficulty in executing activities of daily living) did not present a clear dose-response relationship with polypharmacy. Disability was included in our study as a metric of long-term, cumulative effect from chronic diseases. The relationships were not as marked and not statistically significant, except for 2006 when having disability in five or more activities was associated with 2.4 times higher odds of polypharmacy – as compared to not having any disabilities, and all other things being equal.

Higher income was associated with higher likelihood of polypharmacy in 2000 and 2010. In 2000, each additional R$100 in a person's income was associated with 3.5% greater odds of polypharmacy ($p<0.05$), keeping all other characteristics constant. In 2010 this association, still significant at the $p<0.05$ level, was of a 1% greater odds of polypharmacy. Having health insurance was positively associated with polypharmacy, but only for the two first waves (2000 and 2006) and only at the $p<0.10$ level. The odds of polypharmacy associated with having private health insurance were 42% higher as compared to people without private health insurance in 2000, and 38% higher in 2006, keeping all other factors constant.

There was also a marked, dose-response relationship, between higher health care utilization and polypharmacy. Persons with similar levels of other characteristics who sought more care in the last 12 months had higher odds of polypharmacy. The odds of polypharmacy increased at higher levels of care in all years, although they reached statistical significance only in 2000 and 2010. A person who had one to six medical visits in the last year had 1.5 times higher odds of polypharmacy than a person with no medical visits in 2000, and 2.5 higher odds of polypharmacy in 2010.

Persons with very high health care utilization (over 24 medical visits in the last year) were estimated to have five times higher odds of polypharmacy in 2000 and over seven times higher odds of polypharmacy in 2010, as compared to similar persons with no medical visits in the last year. All relationships were statistically significant at least at the $p<0.05$ level in 2000 and 2010. Again, the relationships were present but less marked in terms of magnitude and statistical significance in 2006.

Having undergone a preventative exam (mammogram for women, prostate exam for men) is another measure of health care utilization. Contrary to the findings on medical visits, having a preventative exam was statistically significantly associated with polypharmacy only in 2006 – in that year, having a preventative exam was associated with 1.7 times higher odds of polypharmacy as compared to not having a preventative exam (all other things being equal). This association was statistically significant at the $p<0.01$ level. The association between preventative exams and polypharmacy was positive in 2000 and 2010 (1.1 times higher odds of polypharmacy in both years), but without statistical significance.

Lastly, behaviors such as smoking and alcohol use were not significantly associated with polypharmacy according to the weighted logistic models.

Table 4.8. Logistic Models Exploring the Association between Polypharmacy and Individual-Level Characteristics

Year	2000 Total N=2143	2006 Total N=1413	2010 Total N=1333
Socio-Demographic			
Age (a)	1.325 (0.087)***	1.164 (0.104)	1.481 (0.094)***
Female gender (b)	1.493 (0.209)*	1.067 (0.195)	0.866 (0.173)
Married (c)	1.183 (0.157)	1.424 (0.177)**	0.981 (0.160)
Per capita income (d)	1.035 (0.015)**	1.010 (0.006)	1.009 (0.004)**
Health insurance (e)	1.430 (0.182)**	1.370 (0.177)*	1.012 (0.165)
Health Status			
Nr. Chronic Diseases (f)	1.764 (0.072)***	1.952 (0.061)***	2.276 (0.062)***
Nr. of Symptoms: 1-2 (g)	2.327 (0.263)***	1.113 (0.217)	1.046 (0.162)
3-5 symptoms	2.710 (0.316)***	1.506 (0.292)	1.449 (0.211)*
6+ symptoms	6.957 (0.440)***	2.195 (0.466)*	2.490 (0.434)**
ADLs w/Disability: 1-4 (h)	1.290 (0.175)	1.189 (0.221)	1.028 (0.163)
5+ ADLs w disability	1.148 (0.255)	2.323 (0.249)***	0.982 (0.270)
Health Utilization			
Medical visits/year: 1-6 (i)	1.490 (0.206)*	1.236 (0.327)	2.530 (0.310)***
6-24 visits	2.376 (0.224)***	2.047 (0.362)**	2.642 (0.377)**
24+ visits	5.254 (0.505)***	2.403 (0.543)	7.198 (0.543)***
Preventative exam (j)	1.139 (0.144)	1.716 (0.200)***	1.137 (0.190)
Behaviors			
Current smoking (k)	0.683 (0.245)	0.703 (0.337)	0.792 (0.230)
Current alcohol use (l)	1.017 (0.214)	0.818 (0.188)	0.797 (0.173)
Constant	0.007 (0.380)***	0.015 (0.422)***	0.023 (0.425)***
Regression Statistics (m)			
N	2126	1350	1309
DF_model	19	18	19
LL	-281150.97	-422112.72	-641654.84
Pseudo R2	0.2327	0.2509	0.2612

Notes:

Logistic regression models weighted by year-specific inverse probability weights. Robust variance estimators. Coefficients are odds ratios, displayed as estimates (standard errors).

* p<0.10; **p<0.05; ***p<0.01

(a) Age calculated in 10-year intervals, centered at age 60.

(b) reference: males

(c) reference: single, widowed or divorced.

(d) Income measured in Brazilian Reais and presented at $100 intervals. Individuals with missing income information (n=631; 13%) were imputed the average per capita income for the corresponding gender and year, and were identified by an indicator variable for missing income. No association between missing income and polypharmacy was found.

(e) Reference: no private health insurance

(f) Chronic diseases: self-reported information on ever having been diagnosed with one or more of the following conditions: hypertension, diabetes, heart disease, lung disease, stroke, cancer, psychiatric conditions, joint diseases, or osteoporosis.

(g) Self-reported information on having experienced persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo, tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence in the last 12 months. Reference: no symptoms.
(h) ADL: activities of daily living. Self-reported information on having difficulty performing one or more of the following activities: walking across a room, getting dressed, bathing, feeding, transferring to/from bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores. Reference: no disability.
(i) Self-reported information of the number of medical visits in the last 12 months. Reference group: no medical visits. There were 348 individuals with missing values for this variable in 2000 (16%). These individuals were identified by an indicator variable for missingness. Missingness was associated with 64% lower odds of polypharmacy ($p<0.05$) in that year. Individuals with missing values in 2006 (N=54, 3.8%) and 2010 (N=4, 0.3%) were not included in the regressions.
(j) Mammogram for women or prostate exam for men. There were 263 individuals (19.7%) with missing values for prevention in 2010. These individuals were identified by an indicator variable for missingness. There was no association between missingness and the odds of polypharmacy in 2010. Individuals with missing values in 2000 (N=14, 0.65%) and 2006 (N=3, 0.21%) were not included in the regressions.
(k) Reference: not currently smoking
(l) Reference: no current use of alcohol
(m) Regression statistics displayed: number of individuals in the regression; number of degrees of freedom in the regression (parameters -1); log-likelihood of the model; pseudo-R squared.

Gender Differences

There is extensive literature demonstrating differences between men and women in the occurrence of polypharmacy. In order to explore whether these differences were associated with other individual characteristics in our sample, we examined the relationships between polypharmacy and individual characteristics separately for men and women. We did this by first analyzing each gender separately (Table 4.9). We also explored interaction terms between each variable and gender. In the case that there are other variables whose relationships with polypharmacy change across genders, this finding may help clarify why the gender differences occur. Table 4.9 displays the gender-specific associations.

Women composed the majority of the sample in all years (59% in 2000, 61% in 2006, and 65% in 2010). The baseline probability of polypharmacy tended to be slightly higher among women. Some variables demonstrated differential associations with polypharmacy across genders: the association between polypharmacy and chronic diseases tended to be lower among women, as was the association with income. Age, health insurance, and care utilization tended to have higher associations with polypharmacy among men. Taken together, the set of individual characteristics tended to explain a higher proportion of the variation in polypharmacy among men than among women (30% vs. 20% in 2000, 27% vs. 24% in 2006, and 32% vs. 22% in 2010) (Table 9).

For a 60-year-old individual who was not married, had no income, no health insurance, no chronic diseases, no symptoms or disabilities, did not have medical visits in the last 12 months, did not undergo preventative exams in the last 24 months and did not smoke or drink, the probability of polypharmacy was 1.3% for women vs. 0.20% for men in 2000, 2.5% or women vs. 0.50% for men in 2006, and 2.8% for women vs. 0.90% for men in 2010.

According to the individual models, chronic diseases were the characteristic most strongly associated with polypharmacy. When men and women were analyzed together, each additional chronic disease was associated with 76% higher odds of polypharmacy in 2000, 95% higher odds in 2006 and 176% higher odds in 2010 (all other things being equal) (Table 2A). When women and men were analyzed separately a gender-specific association between chronic diseases and polypharmacy was identified. Although higher numbers of chronic conditions were associated with higher odds of polypharmacy in both genders, this association was lower for women in all years. All other variables did not have significant interaction terms with gender.

In 2000, each additional chronic disease was associated with 132% higher odds of polypharmacy among men. Among women, however, each additional chronic disease was associated with 60% higher odds of polypharmacy, all other things being equal. In 2006, the difference between men and women decreased slightly: men had an average of 122% higher odds of polypharmacy for each additional chronic disease and women had 80%. In 2010 the difference increased significantly. Each additional chronic disease was associated with 210% higher odds of polypharmacy among men but 101% higher odds among women, all other things being equal. All associations were statistically significant at the $p<0.001$ level.

Gender differences in the effect of chronic diseases with polypharmacy were also captured by an interaction term between chronic diseases and female gender in the overall logistic individual models, which was smaller than zero (indicating lower magnitude among women as compared to men) and statistically significant in the three survey years.

Age and medical care worked differently. In 2000, each additional year of age was associated with on average 4% higher odds of polypharmacy among women (statistically significant at the $p<0.01$ level), and 2% higher odds among men (not statistically significant). In 2010, each additional year of age was associated with on

average 5% higher odds of polypharmacy among women (statistically significant at the $p<0.01$ level), and 4% higher odds among men (statistically significant at the $p<0.05$ level), all other things being equal.

Medical care, as measured by the number of medical visits in the last 12 months, was associated with higher odds of polypharmacy among women. The association was verified in 2000 and 2010, but not in 2006. The greater the care utilization, the greater the difference in effects comparing women to men. At lower levels of care (1-6 medical visits per year), there tended to be a minimal difference between genders (less than 1%), where men even tended to have higher magnitude of effects than women. At higher levels of care (6-24 visits and above 24 visits a year) the association with polypharmacy was much greater among women. It is possible that this reflects the small sample size of the group of men, but it should be further investigated. When measured by having undergone a preventative exam in the last 12 months women tended to have smaller odds of polypharmacy than men. However, with the exception of 2006 the associations were not statistically significant at the significance level $p<0.05$.

The associations of both age and medical care utilization were positive when investigated through interaction terms added to the overall logistic individual models. However, the interaction terms were not statistically significant. We hypothesize that differences in the sample sizes between women and men, and especially between genders for each category of age and medical care utilization (both of which have a predominance of women in their highest levels) might help explain why the interaction terms lacked statistical significance.

Health insurance tended to have larger (more positive) associations with the odds of polypharmacy among women, but income levels tended to have lower (less positive) associations among women. These findings are surprising because income and private health insurance are highly correlated and can be interpreted to represent higher purchasing power, and therefore would be expected to behave similarly. Their different associations with gender raises questions related to the relative importance of greater purchasing power (as identified by higher income levels) versus greater access to care (as identified by higher health insurance coverage) across genders, and warrant future investigation.

Table 4.9 Gender-Specific Analyses of the Links between Polypharmacy and Individual Characteristics

Year	2000		2006		2010	
	Women	Men	Women	Men	Women	Men
Socio-Demographic						
Age (a)	1.361 (0.114)***	1.189 (0.155)	1.143 (0.150)	1.160 (0.172)	1.506 (0.109)***	1.404 (0.157)**
Married (c)	1.069 (0.192)	2.344 (0.379)**	1.241 (0.239)	2.238 (0.396)**	0.924 (0.197)	1.149 (0.344)
Per capita income (d)	1.030 (0.015)*	1.057 (0.024)**	1.005 (0.007)	1.020 (0.008)**	1.010 (0.005)**	1.008 (0.010)
Health insurance (e)	1.618 (0.209)**	0.906 (0.331)	1.466 (0.221)*	1.257 (0.325)	0.919 (0.189)	1.276 (0.286)
Health Status						
Nr. Chronic Diseases (f)	1.630 (0.077)***	2.325 (0.151)***	1.841 (0.071)***	2.223 (0.132)***	2.011 (0.074)***	3.103 (0.129)***
Nr. of Symptoms: 1-2 (g)	2.046 (0.289)**	3.202 (0.456)**	0.914 (0.269)	1.543 (0.335)	0.957 (0.222)	1.231 (0.329)
3-5 symptoms	2.386 (0.325)***	4.144 (0.557)**	1.355 (0.348)	1.587 (0.465)	1.283 (0.258)	1.933 (0.399)*
6+ symptoms	5.479 (0.470)***	17.441 (0.920)**	1.403 (0.578)	5.374 (0.746)**	1.667 (0.443)	1.000 (0.000)
ADLs w/Disability: 1-4 (h)	1.394 (0.214)	0.903 (0.361)	1.213 (0.262)	1.207 (0.371)	1.130 (0.186)	0.808 (0.320)
5+ ADLs w disability	1.177 (0.284)	1.268 (0.588)	2.649 (0.292)***	2.061 (0.473)	1.212 (0.312)	0.507 (0.460)
Health Utilization						
Medical visits/year: 1-6 (i)	1.703 (0.255)**	1.177 (0.371)	0.974 (0.443)	1.807 (0.531)	2.773 (0.381)***	2.276 (0.496)*
6-24 visits	2.614 (0.234)***	2.384 (0.438)**	1.958 (0.495)	1.918 (0.566)	2.808 (0.446)**	2.764 (0.731)
24+ visits	8.159 (0.579)***	2.429 (0.981)	2.910 (0.693)	1.451 (1.034)	16.397 (0.608)**	2.420 (0.792)
Preventative exam (j)	0.999 (0.185)	1.728 (0.304)*	1.721 (0.218)**	1.767 (0.340)*	0.966 (0.205)	1.693 (0.363)
Behaviors						
Current smoking (k)	0.673 (0.317)	0.788 (0.439)	0.461 (0.413)*	1.216 (0.484)	0.703 (0.286)	0.941 (0.533)
Current alcohol use (l)	0.968 (0.254)	1.190 (0.343)	0.848 (0.239)	0.778 (0.335)	0.911 (0.231)	0.614 (0.277)*
Constant	0.013 (0.377)***	0.002 (0.837)***	0.026 (0.525)***	0.005 (0.707)***	0.029 (0.449)***	0.009 (0.804)***
Regression Statistics (m)						
N	1253	873	830	520	841	460
Pseudo R2	0.200	0.303	0.243	0.272	0.216	0.320

Notes:

Logistic regression models weighted by year-specific inverse probability weights. Robust variance estimators. Coefficients are odds ratios, displayed as estimates (standard errors). * p<0.10; **p<0.05; ***p<0.01

(a) Age calculated in 10-year intervals, centered at age 60.

(b) reference: males

(c) reference: single, widowed or divorced.

(d) Income measured in Brazilian Reais and presented at $100 intervals. Individuals with missing income information (n=631; 13%) were imputed the average per capita income for the corresponding gender and year, and were identified by an indicator variable for missing income. No association between missing income and polypharmacy was found.

(e) Reference: no private health insurance

(f) Chronic diseases: self-reported information on ever having been diagnosed with one or more of the following conditions: hypertension, diabetes, heart disease, lung disease, stroke, cancer, psychiatric conditions, joint diseases, or osteoporosis.

(g) Self-reported information on having experienced persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo, tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence in the last 12 months. Reference: no symptoms.

(h) ADL: activities of daily living. Self-reported information on having difficulty performing one or more of the following activities: walking across a room, getting dressed, bathing, feeding, transferring to/from bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores. Reference: no disability.

(i) Self-reported information of the number of medical visits in the last 12 months. Reference group: no medical visits. There were 348 individuals with missing values for this variable in 2000 (16%). These individuals were identified by an indicator variable for missingness. Missingness was associated with 64% lower odds of polypharmacy (p<0.05) in that year. Individuals with missing values in 2006 (N=54, 3.8%) and 2010 (N=4, 0.3%) were not included in the regressions.

(j) Mammogram for women or prostate exam for men. There were 263 individuals (19.7%) with missing values for prevention in 2010. These individuals were identified by an indicator variable for missingness. There was no association between missingness and the odds of polypharmacy in 2010. Individuals with missing values in 2000 (N=14, 0.65%) and 2006 (N=3, 0.21%) were not included in the regressions.

(k) Reference: not currently smoking

(l) Reference: no current use of alcohol

(m) Regression statistics displayed: number of individuals in the regression; number of degrees of freedom in the regression (parameters -1); log-likelihood of the model; pseudo-R squared.

Comparison between Logistic and Multi-Level Latent and Mixed Effects Models

Multi-level regression models take into consideration the correlations that may exist between individuals living in the same geographic area. Individuals living in the same area may share exposures and circumstances that may influence their likelihood of polypharmacy in addition to what is determined by their personal exposures and characteristics. This aggregation is not taken into consideration by regular logistic regression models. When the correlation between individuals living in the same area is not accounted for in the analytical models, the assumption of independence between observations may be violated, and the estimates may be biased.

The nature of our investigation, where we seek to ultimately parse out the association of geographic and individual characteristics to the odds of polypharmacy, requires that we consider the aggregation at the geographic level even when we investigate individual-level characteristics. Table 4.10 displays the results of multi-level latent and mixed effects regression models in comparison to logistic regression models.

The main effect introduced by the multi-level models is the estimation of a random intercept at the area level. In the multi-level model the baseline propensity for polypharmacy for individuals living in each of the areas is captured by the area-level random intercept. It is assumed that individuals are independent from each other once the correlation between them is accounted for.

The results from the two different models were qualitatively similar. Higher age, female gender, higher income, access to health insurance, greater health care utilization and lower health status were each independently associated with higher odds of polypharmacy. The multi-level model also found a difference in the effect of chronic diseases according to gender, where each additional chronic disease tended to be associated with higher odds of polypharmacy for both genders, but among women the associations tended to be of lower magnitude than among men.

There was no major quantitative difference in the estimation of the fixed effects of the individual level variables between the multi-level and the logistic models. Both models tended to agree on the direction and the statistical

significance of the majority of the variables investigated. With few exceptions the multi-level estimates tended to have lower magnitude than the logistic estimates, suggesting that not accounting for the area-level correlation between individuals introduced a small but positive bias in the estimation of most effects.

Table 4.10 Comparison between Logistic and Multi-Level Generalized Latent Mixed Regression Models Exploring the Association between Polypharmacy and Individual-level Characteristics

Year	2000		2006		2010	
	LOGISTIC	GLLAMM	LOGISTIC	GLLAMM	LOGISTIC	GLLAMM
Socio-Demographic						
Age (a)	1.325 (0.087)***	1.275 (0.086)***	1.164 (0.104)	1.096 (0.095)	1.481 (0.094)***	1.439 (0.103)***
Female gender (b)	1.493 (0.209)*	1.430 (0.165)**	1.067 (0.195)	0.992 (0.192)	0.866 (0.173)	0.833 (0.175)
Married (c)	1.183 (0.157)	1.148 (0.161)	1.424 (0.177)**	1.333 (0.158)*	0.981 (0.160)	0.998 (0.139)
Per capita income (d)	1.035 (0.015)**	1.032 (0.006)***	1.010 (0.006)	1.007 (0.006)	1.009 (0.004)**	1.007 (0.004)*
Health insurance (h)	1.430 (0.182)**	1.364 (0.206)	1.370 (0.177)*	1.161 (0.155)	1.012 (0.165)	0.849 (0.164)
Health Status						
Nr. Chronic Diseases (e)	1.764 (0.072)***	1.779 (0.067)***	1.952 (0.061)***	2.027 (0.073)***	2.276 (0.062)***	2.335 (0.055)***
Nr. of Symptoms: 1-2 (f)	2.327 (0.263)***	2.304 (0.195)***	1.113 (0.217)	1.192 (0.219)	1.046 (0.162)	1.109 (0.167)
3-5 symptoms	2.710 (0.316)***	2.775 (0.277)***	1.506 (0.292)	1.576 (0.298)	1.449 (0.211)*	1.494 (0.192)**
6+ symptoms	6.957 (0.440)***	6.649 (0.401)***	2.195 (0.466)*	2.189 (0.551)	2.490 (0.434)**	2.690 (0.393)**
ADLs w/Disability: 1-4 (g)	1.290 (0.175)	1.300 (0.166)	1.189 (0.221)	1.294 (0.257)	1.028 (0.163)	1.099 (0.150)
5+ ADLs w disability	1.148 (0.255)	1.193 (0.256)	2.323 (0.249)***	2.493 (0.268)***	0.982 (0.270)	0.999 (0.248)
Health Utilization						
Medical visits/year: 1-6 (i)	1.490 (0.206)*	1.520 (0.200)**	1.236 (0.327)	1.293 (0.281)	2.530 (0.310)***	2.812 (0.307)***
6-24 visits	2.376 (0.224)***	2.468 (0.283)***	2.047 (0.362)**	2.253 (0.293)***	2.642 (0.377)**	3.155 (0.357)***
24+ visits	5.254 (0.505)***	5.368 (0.551)***	2.403 (0.543)	3.167 (0.447)***	7.198 (0.543)***	7.939 (0.542)***
Preventative exam (j)	1.139 (0.144)	1.157 (0.148)	1.716 (0.200)***	1.788 (0.173)***	1.137 (0.190)	1.164 (0.194)
Behaviors						
Current smoking (k)	0.683 (0.245)	0.673 (0.212)*	0.703 (0.337)	0.709 (0.351)	0.792 (0.230)	0.807 (0.248)
Current alcohol use (l)	1.017 (0.214)	0.989 (0.196)	0.818 (0.188)	0.733 (0.165)*	0.797 (0.173)	0.752 (0.139)**
Constant	0.007 (0.380)***	0.007 (0.386)***	0.015 (0.422)***	0.011 (0.292)***	0.023 (0.425)***	0.019 (0.411)***
Regression Statistics (m)						
N	2126	2126	1350	1350	1309	1309
DF_model / Nr. Parameters	19	21	18	20	19	21
LL	-281150.97	-276188.21	-422112.72	-400121.2	-641654.84	-626061.56
Pseudo R2 / RI Var(se)	0.233	0.091 (0.017)	0.251	0.174 (0.025)	0.261	0.184 (0.034)

Notes:

Logistic regression models weighted by year-specific inverse probability weights. Robust variance estimators. GLLAMM: Multi-level generalized latent mixed regression models weighted by year-specific inverse probability weights. Include random intercept at the area level. Robust variance estimators.

Coefficients are odds ratios, displayed as estimates (standard errors).

* p<0.10; **p<0.05; ***p<0.01

(a) Age calculated in 10-year intervals, centered at age 60.

(b) reference: males

(c) reference: single, widowed or divorced

(d) Income measured in Brazilian Reais and presented at $100 intervals. Individuals with missing income information (n=631; 13%) were imputed the average per capita income for the corresponding gender and year, and were identified by an indicator variable for missing income. A statistically significant association at the 0.05 level between missing income and polypharmacy was found in 2010, where individuals with missing income had 0.8% higher odds of polypharmacy. No relevant associations were found between missing income and polypharmacy in the other two years.

(e) Reference: no private health insurance

(f) Chronic diseases: self-reported information on ever having been diagnosed with one or more of the following conditions: hypertension, diabetes, heart disease, lung disease, stroke, cancer, psychiatric conditions, joint diseases, or osteoporosis.

(g) Self-reported information on having experienced persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo, tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence in the last 12 months. Reference: no symptoms.
(h) ADL: activities of daily living. Self-reported information on having difficulty performing one or more of the following activities: walking across a room, getting dressed, bathing, feeding, transferring to/from bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores. Reference: no disability.
(i) Self-reported information of the number of medical visits in the last 12 months. Reference group: no medical visits. There were 348 individuals with missing values for this variable in 2000 (16%). These individuals were identified by an indicator variable for missingness. Missingness was associated with 63% lower odds of polypharmacy ($p<0.05$) in that year. Individuals with missing values in 2006 (N=54, 3.8%) and 2010 (N=4, 0.3%) were not included in the regressions.
(j) Mammogram for women or prostate exam for men. There were 263 individuals (19.7%) with missing values for prevention in 2010. These individuals were identified by an indicator variable for missingness. There was no statistically significant association between missingness and the odds of polypharmacy in 2010. Individuals with missing values in 2000 (N=14, 0.65%) and 2006 (N=3, 0.21%) were not included in the regressions.
(k) Reference: not currently smoking
(l) Reference: no current use of alcohol
(m) Regression statistics displayed: number of individuals in the regression; number of degrees of freedom (parameters - 1) for the logistic model, number of parameters for the GLLAMM model; log-likelihood of the model; pseudo-R squared for the logistic model and variance and standard error of the random intercept for the GLLAMM model.

4.4.3 Part 3 – Geographic Variation in Polypharmacy and Association with Community-Level Characteristics

We first explored the geographic patterns of polypharmacy by aggregating individuals into the 30 geographic sub-divisions of the city of Sao Paulo (sub-prefectures). We were interested in identifying the extent of clustering in the patterns of polypharmacy across the geographic areas. We implemented multi-level generalized latent mixed regression models where we estimated a random intercept at the area level and we assumed an exchangeable correlation pattern among subjects living in the same area. Similarly to the logistic models, we also utilized inverse-probability weights in order to reconstruct the population of Sao Paulo in each of the years.

We implemented "null" models without covariates in order to capture the extent of variation across areas (Table 4.11). We obtained the probability of polypharmacy from the baseline log odds from each model. We found an estimated average prevalence of polypharmacy at the sub-prefecture level of 16.5% in 2000, 25.5% in 2006 and 38% in 2010. These values are similar to the estimates from the weighted logistic regressions (the differences being around 0.4-0.5%).

From the multi-level models, we calculated the 95% confidence interval for the baseline prevalence of polypharmacy. We found that 95% of the sub-prefectures have baseline prevalence of polypharmacy estimated between 10.4%-25.3% in 2000, 12.3%-45.5% in 2006, and 26.9%-50.5% in 2010.

Using the multi-level models we also calculated the intraclass correlation coefficient (ICC) for each of the years. The ICC estimates the correlation between observations within a same cluster. The ICC was very low in all years, indicating that there was a very small correlation in terms of the likelihood of polypharmacy between individuals of the same cluster. This indicates that most of the variation in the odds of polypharmacy is driven by characteristics pertaining to individuals, and not by different propensities at the area level. This very low correlation was consistent across the survey waves.

Table 4.11 Aggregation and Geographic Variation in Polypharmacy

	Average (95% CI) polypharmacy		Weighted Gllamm	
Year	Weighted Logistic	Weighted Gllamm	Random Intercepts: Avg (95% CI)	ICC
2000	0.161 (0.146–0.178)	0.165 (0.157–0.173)	0.165 (0.104–0.253)	0.022
2006	0.260 (0.232–0.291)	0.255 (0.247–0.264)	0.255 (0.123–0.455)	0.059
2010	0.376 (0.343–0.411)	0.380 (0.373–0.387)	0.380 (0.269–0.505)	0.020

Notes:

Models are devoid of covariates and weighted by inverse probability weights at the individual level. Gllamm: multi-level generalized latent mixed regression model; includes random intercept for area (sub-prefecture) and assumes exchangeable correlation across observations from the same area. ICC: Intra-class correlation coefficient. 95%CI: confidence interval comprehending 95% of values around the average.

Links between Community-Level Characteristics and Area-Level Odds of Polypharmacy

We explored the associations between polypharmacy and geographic-level characteristics through two main methodological approaches. First we used geographic characteristics to model average likelihood of polypharmacy at the geographic level. This is important in order to understand which characteristics at the area level may be related to polypharmacy. However, because both sides of the analysis (outcomes and exposures) are used in an aggregated form this approach can often give rise to an ecological fallacy. An ecological fallacy happens when inferences about individuals are made based on analysis of aggregated data. In this case, inferences may be incorrect because it is not possible to ascertain which individuals were exposed and which developed the outcome. We evaluated the association between geographic-level characteristics and polypharmacy measured at the individual level in separate models (Table 4.11).

Because the number of geographic areas was small (n=30) we utilized "count" versions of the variables "number of symptoms" and "number of ADLs with disabilities", and we utilized a binary version of the variable "health care utilization". We favored this approach out of concern about having an excessive number of parameters in our models, given the small number of geographic units that limit the degrees of freedom of the model. The results from the aggregated geographic models are displayed in Table 12.

The models estimate the baseline odds of polypharmacy at the area level (constant terms), which we can transform into a probability. The baseline probability of polypharmacy was 0.04% in 2000, 1% in 2006 and 5.3% in 2010 for an area where the senior population had average age of 60 years, where all the individuals were men and none was married, where the prevalence of smoking and alcohol were zero, the average per capita income was zero and no one had health insurance, where people had on average no chronic diseases, no symptoms and no disabilities, where average health care utilization was low or none, and where no persons had undergone preventative exams (Table 4.12).

Results from multi-level generalized latent mixed-effects regression models of the Odds of Polypharmacy Measured at the Geographic Area-Level

Table 4.12 Links between Polypharmacy and Geographic Characteristics

Year	2000			2006			2010		
Area Level Characteristics	Odds Ratios	95% Conf.Interval	p-value	Odds Ratios	95% Conf.Interv	p-value	Odds Ratios	95% Conf.Interval	p-value
Average age (a)	1.06	(0.89–1.24)	0.504	1.90	(1.53–2.35)	<0.001	1.32	(1.19–1.47)	<0.001
% women	35.5	(19.65–64.23)	<0.001	0.252	(0.14–0.46)	<0.001	0.51	(0.31–0.83)	0.007
% married (b)	5.00	(2.90–8.63)	<0.001	1.21	(0.71–2.05)	0.488	0.566	(0.401–0.80)	0.001
Avg. per capita income (c)	0.91	(0.87–0.93)	<0.001	0.964	(0.95–0.99)	<0.001	1.05	(1.04–1.06)	<0.001
% health insurance (d)	1.01	(0.74–1.36)	0.948	3.69	(2.79–4.8)	<0.001	0.546	(0.416–0.719)	<0.001
Avg. nr. chronic diseases (e)	1.09	(0.89–1.32)	0.375	2.45	(1.82–3.29)	<0.001	2.08	(1.78–2.42)	<0.001
Avg. nr. symptoms (f)	0.634	(0.56–0.71)	<0.001	0.847	(0.75–0.96)	0.006	0.903	(0.794–1.03)	0.12
Avg. nr. ADLs w/disability (g)	2.36	(2.16–2.57)	<0.001	1.03	(0.86–1.23)	0.759	1.05	(0.985–1.11)	0.148
% mod-high care users (h)	12.3	(7.14–21.34)	<0.001	2.00	(1.39–2.86)	<0.001	0.751	(0.467–1.21)	0.237
% preventative care (i)	5.93	(3.37–10.44)	<0.001	0.945	(0.45–1.97)	0.88	2.86	(1.59–5.15)	<0.001
% smoking (j)	0.049	(0.03–0.09)	<0.001	4.17	(1.69–10.26)	0.002	1.46	(0.71–3.0)	0.305
% alcohol use (k)	64.42	(31.8–130.4)	<0.001	2.26	(1.64–3.10)	<0.001	0.364	(0.267–0.497)	<0.001
Constant term	0.0004	(0.000–0.001)	<0.001	0.01	(0.004–0.02)	<0.001	0.056	(0.034–0.091)	<0.001
Nr. subjects (nr. areas)		2126 (27)			1350 (30)			1309 (30)	
Parameters		14			14			14	
LL		-8638.4778			-5398.2242			-6106.0701	
RE Var (se)		0.102 (0.016)			0.127 (0.021)			0.074 (0.016)	

Notes:

Multi-level generalized latent mixed regression models include random intercept at the area level (subprefecture). Models are not weighted. Estimates are odds ratios, presented with 95% confidence intervals and significance levels (p-value)
Outcome: average odds of polypharmacy at the area level
Area-level variables calculated from the data from the SABE survey, and reflect year-specific averages for the population of 60-year olds and over in each of the geographic areas.
(a) Age calculated in 10-year intervals, centered at age 60.
(b) Reference: not currently married or in a civil union.
(c) Income measured in Brazilian Reais and presented at $100 intervals.
(d) Chronic diseases: self-reported information on ever having been diagnosed with one or more of the following conditions: hypertension, diabetes, heart disease, lung disease, stroke, cancer, psychiatric conditions, joint diseases, or osteoporosis.
(e) Reference: no private health insurance
(f) Self-reported information on having experienced persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo, tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence in the last 12 months.
(g) ADL: activities of daily living. Self-reported information on having difficulty performing one or more of the following activities: walking across a room, getting dressed, bathing, feeding, transferring to/from bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores.
(h) Self-reported information of the number of medical visits in the last 12 months. Moderate-high utilization: 7 or more medical visits. Reference: 0-6 medical visits.
(i) Self-report of having undergone mammogram (women) or prostate exam (men) in the last 24 months.
(j) Reference: not currently smoking
(k) Reference: no current use of alcohol

The models estimate associations between community-level characteristics and the average odds of polypharmacy at the community level. Each coefficient represents the expected change in the average odds of polypharmacy associated with a one-unit change in the average level of the covariate in an area with average rates of polypharmacy.

All variables exhibited some degree of relevant association with average odds of polypharmacy at the area level. Average age, average number of chronic diseases, and average levels of disability were consistently associated with higher odds of polypharmacy in all years. Higher levels of symptoms were consistently associated with lower odds of polypharmacy at the community level in all years. Average income had an association that, although statistically significant in all years, was very close to 1.

Other characteristics, especially those that represented percentages, had associations that changed in both magnitude and direction across the survey waves. A one-unit change in covariates that are percentages (such as percentage of married individuals and percentage of women) represents a change of 100% in that covariate. Coefficients in our models therefore represent the expected change in the odds of polypharmacy comparing areas with 100% vs. zero% of each characteristic.

Some of these comparisons may not be applicable in real life. For example, it is virtually impossible that any of the Sao Paulo sub-prefectures, which according to our data had about 400 thousand inhabitants on average, would actually have the entirety of their senior population composed of women or men. These comparisons may also represent large extrapolations from our data, aggravated by the small number of geographic areas (total of 30 units).

Also, characteristics such as female gender, higher age and married status tend to be correlated. Multicollinearity across variables may further help explain the changes in magnitude and direction of associations. In order to explore that, we analyzed each of the area-level covariates in a univariate regression model (Table 4.13).

Table 4.13 Independent effect of area-level characteristics on the area-level odds of polypharmacy – ***Each row represents a different regression model that includes only the listed covariate***

Year	2000			2006			2010		
Area Level Characteristics	Odds Ratios	95% Conf.Interval	p-value	Odds Ratios	95% Conf.Interval	p-value	Odds Ratios	95% Conf.Interval	p-value
Average age (a)	1.97	(1.80– 2.14)	<0.001	1.42	(1.32– 1.53)	<0.001	1.55	(1.42– 1.69)	<0.001
% women	45.3	(33.21–61.79)	<0.001	0.97	(0.72– 1.29)	0.81	2.07	(1.37– 3.13)	0.001
% married (b)	0.24	(0.20– 0.30)	<0.001	0.22	(0.17– 0.29)	<0.001	0.18	(0.13– 0.25)	<0.001
Avg. per capita income (c)	1.05	(1.05– 1.06)	<0.001	1.02	(1.01– 1.03)	<0.001	1.03	(1.03– 1.04)	<0.001
% health insurance (d)	1.98	(1.82– 2.16)	<0.001	3.35	(2.94– 3.82)	<0.001	2.17	(1.91– 2.47)	<0.001
Avg. nr. chronic diseases (e)	3.98	(3.56– 4.46)	<0.001	3.82	(3.25– 4.50)	<0.001	1.6	(1.44– 1.78)	<0.001
Avg. nr. symptoms (f)	1.08	(1.03– 1.14)	0.002	1.21	(1.12– 1.30)	<0.001	1.34	(1.25– 1.44)	<0.001
Avg. nr. ADLs w/disability (g)	1.16	(1.12– 1.20)	<0.001	1.29	(1.24– 1.34)	<0.001	1.1	(1.06– 1.15)	<0.001
% mod-high care users (h)	2.53	(1.59– 4.01)	<0.001	1.67	(1.44– 1.94)	<0.001	1.71	(1.15– 2.54)	0.008
% preventative care (i)	7.51	(5.96– 9.46)	<0.001	10.38	(7.01–15.37)	<0.001	0.57	(0.42– 0.77)	<0.001
% smoking (j)	0.02	(0.01– 0.03)	<0.001	0.01	(0.01– 0.02)	<0.001	0.12	(0.07– 0.20)	<0.001
% alcohol use (k)	6.49	(4.98– 8.45)	<0.001	2.04	(1.65– 2.53)	<0.001	1.01	(0.82– 1.24)	0.937

Notes: Same as Table 4.12.

Next we analyzed the association between area-level characteristics and the odds of polypharmacy at the individual level (Table 4.14). The findings from the models analyzing outcomes at the individual level were similar to those analyzing the outcome at the area-level. However, there were more data points contributing to the estimation in this model, which improved the efficiency of some of the estimates but not all of them.

Table 4.14 Links between Polypharmacy and Geographic Characteristics: Results from multi-level generalized latent mixed-effects regression models of the Odds of Polypharmacy Measured at the Individual Level

Year / Area Level Characteristics	2000 Odds Ratios	2000 95% Conf.Interval	2000 p-value	2006 Odds Ratios	2006 95% Conf.Interval	2006 p-value	2010 Odds Ratios	2010 95% Conf.Interval	2010 p-value
Average age (a)	1.39	(1.08– 1.79)	0.012	0.73	(0.65– 0.80)	<0.001	1.42	(1.31– 1.53)	<0.001
% women	2.57	(1.34– 4.93)	0.004	0.24	(0.16– 0.35)	<0.001	1.36	(0.98– 1.88)	0.064
% married (b)	2.79	(1.43– 5.44)	0.003	24.31	(14.42–40.98)	<0.001	1.71	(1.43– 2.04)	<0.001
Avg. per capita income (c)	0.93	(0.89– 0.97)	0.001	0.94	(0.93– 0.95)	<0.001	0.99	(0.98– 0.99)	0.001
% health insurance (d)	1.15	(0.77– 1.73)	0.492	2.73	(2.36– 3.17)	<0.001	3.49	(2.71– 4.48)	<0.001
Avg. nr. chronic diseases (e)	1.13	(0.93– 1.38)	0.227	1.15	(0.94– 1.41)	0.162	1.85	(1.66– 2.08)	<0.001
Avg. nr. symptoms (f)	1.18	(0.94– 1.47)	0.153	1.41	(1.26– 1.57)	<0.001	0.98	(0.88– 1.09)	0.769
Avg. nr. ADLs w/disability (g)	0.9	(0.83– 0.98)	0.011	1.41	(1.30– 1.54)	<0.001	0.78	(0.73– 0.82)	<0.001
% mod-high care users (h)	10.74	(4.42–26.11)	<0.001	0.97	(0.82– 1.15)	0.762	1.05	(0.67– 1.65)	0.825
% preventative care (i)	1.85	(0.90– 3.77)	0.092	15.96	(9.51–26.78)	<0.001	0.74	(0.45– 1.22)	0.241
% smoking (j)	0.57	(0.28– 1.15)	0.116	0.01	(0.01– 0.02)	<0.001	1.33	(0.78– 2.27)	0.296
% alcohol use (k)	1.12	(0.60– 2.07)	0.726	3.05	(2.34– 3.99)	<0.001	0.57	(0.47– 0.69)	<0.001
Constant term	0.005	(0.002– 0.01)	<0.001	0.008	(0.005– 0.01)	<0.001	0.07	(0.05– 0.11)	<0.001
Nr. subjects (nr. areas)			2126			1350			1309
Parameters			14			14			14
LL			-359273.15			-540138.46			-849544.43
RE Var (se)			0.208 (0.025)			0.080 (0.012)			0.050 (0.012)

Notes:

Multi-level generalized latent mixed regression models include random intercept at the area level (subprefecture). Models are not weighted.

Estimates are odds ratios, presented with 95% confidence intervals and significance levels (p-value)

Outcome: average odds of polypharmacy at the area level

Area-level variables calculated from the data from the SABE survey, and reflect year-specific averages for the population of 60-year olds and over in each of the geographic areas.

(a) Age calculated in 10-year intervals, centered at age 60.

(b) Reference: not currently married or in a civil union.

(c) Income measured in Brazilian Reais and presented at $100 intervals.

(d) Chronic diseases: self-reported information on ever having been diagnosed with one or more of the following conditions: hypertension, diabetes, heart disease, lung disease, stroke, cancer, psychiatric conditions, joint diseases, or osteoporosis.

(e) Reference: no private health insurance

(f) Self-reported information on having experienced persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo, tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence in the last 12 months.

(g) ADL: activities of daily living. Self-reported information on having difficulty performing one or more of the following activities: walking across a room, getting dressed, bathing, feeding, transferring to/from bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores.

(h) Self-reported information of the number of medical visits in the last 12 months. Moderate-high utilization: 7 or more medical visits. Reference: 0-6 medical visits.

(i) Self-report of having undergone mammogram (women) or prostate exam (men) in the last 24 months.

(j) Reference: not currently smoking

(k) Reference: no current use of alcohol

4.4.4 Part 4 – Association between Polypharmacy and Community Characteristics Controlling for Individual Characteristics (Contextual and Compositional Effects)

In order to investigate for the effects of community-level variables on the odds of polypharmacy we implement a series of models where we assess the relationship between polypharmacy and the different area-level factors, controlling for all individual-level characteristics examined in the previous section.

It is important to note that the current section and the next one describe results from conditional models (generalized latent and mixed-effects models). The interpretation of the results of conditional models reflects the associations occurring at **areas with the average outcome** (average rates of polypharmacy). The effects are not marginal, and they do not necessarily have the same size or sign at different points of the outcome distribution. This is different from what would be expected to have in a linear regression analysis and will be reiterated ahead.

The analysis of the multiple area-level characteristics elicits a pattern suggesting that area-level characteristics may also represent predisposing, enabling, and illness levels factors, which can be associated with the likelihood of polypharmacy independently from the individual characteristics.

Table 4.15 displays the main results from this analysis. Each of the area-level variables was included in a model containing all individual-level characteristics but no other community-level characteristic, to avoid multicollinearity. Because we anticipate the possibility of measurement errors, we also investigated variables collected from other sources external to the SABE survey. We sought to obtain greater validity of our findings by examining multiple correlates of a same concept. Also, we sought to examine the multiple area-level characteristics in order to define which would be more appropriate to include in a full model. We display all measures that we analyzed, classified according to their category in the conceptual framework.

We find that characteristics that identified an older and predominantly female composition of the population– the predisposing factors – tended to be positively associated with polypharmacy. These variables indicate that two individuals who share all the same individual-level characteristics but that live in areas that have different levels of aging individuals tend to exhibit different likelihood of polypharmacy according to the area-level

composition. The person who lives in an area with greater percentage of seniors, greater average age, or greater proportion of women (which, among seniors, is a proxy for older age) will be expected to have greater likelihood of polypharmacy.

Variables indicative of higher illness levels in the population exhibited a different pattern: higher mortality tended to be associated with higher rates of polypharmacy, whereas greater number of chronic diseases, higher disability and higher levels of symptoms tended to be associated with lower polypharmacy. It is possible that these metrics correspond to different concepts. For example, areas with higher mortality may have especially high diseases lethality from certain conditions. Perhaps the same conditions yield less risk of death in other geographic areas. – For example, stroke, can be very lethal if there is no adherence to pharmacologic treatments, or low supportive care and monitoring. In areas where providers anticipate that there is elevated risk of a bad outcome from a stroke, the prescribed may be motivated to treat the stroke and its underlying conditions more aggressively.

It is also possible that our disease metrics - greater number of chronic diseases, higher disability and higher levels of symptoms – may reflect community-level levels of disease morbidity. Perhaps providers working in areas with greater disease morbidity and greater disability may anticipate that their patients will be frail and therefore be motivated to prescribe less aggressively.

Measures of higher socio-economic status of a community tended to support a positive association with polypharmacy. Individuals with same personal characteristics who differ only from living in an urban or predominantly rural area can be expected to have different odds of polypharmacy. All other things being equal, a person living in a predominantly rural area is expected to have about 48% lower odds of polypharmacy in 2000 and 42% lower odds in 2010 than a person living in an urban area, as long both areas have average levels of the outcome.

Average area-level per capita income was positively associated with the odds of polypharmacy, as was higher prevalence of health insurance among seniors. These findings indicate that, from two individual with same personal characteristics living in areas that differ only by their prevalence of heath insurance, the individual living in an area where all seniors have health insurance would have eight times greater odds (in 2006) and

about five times greater odds of polypharmacy (in 2010) than the individual living in an area where no seniors have health insurance. These findings suggest that the resources at the area level may play a significant role in determining an individual's likelihood of polypharmacy, in excess of an individual's personal resources.

Areas with greater private health insurance coverage also tended to have greater levels of polypharmacy. In fact, the coefficients associated with high health insurance coverage represent the largest magnitudes across all community-level variables. We attempt to clarify this association by controlling for confounding between the diverse level-2 variables in a multi-variate model described below.

Lastly, the findings related to health care utilization do not form a clear pattern. Hospital admissions indicate a positive relationship with polypharmacy, but utilizing high levels of medical care has conflicting results between 2000 and 2006.

The effect of seeking physician care was positively associated with polypharmacy at the individual level, indicating that a person who sought more care (all other things being equal) had greater odds of having polypharmacy than a person who sought less care.

At the area level, however, higher rates of health care utilization suggested an association with lower odds of polypharmacy. This indicates that if two individuals with similar personal characteristics live in areas that differ in the rates of health care utilization (but have similar other area-level characteristics), the odds of polypharmacy would be expected to be lower for the individual who lives in an area with greater health care utilization.

It is possible that these metrics indicate differences in polypharmacy according to the type of service reviewed. It is also possible that these characteristics are "proxies" for other characteristics of health care – greater availability, or greater quality of care, for example. These, however, are speculations. We perform an empirical investigation of this possibility in the next chapter.

Table 4.15 Association between polypharmacy and each community-area characteristic, controlling for individual-level factors

		2000	2006	2010
PREDISPOSING	Avg. Age	2.7	2.13***	1.21
		(0.36–20.35)	(1.65–2.74)	(0.87–1.68)
	% seniors	7.62***	60.08***	70.47***
		(2.02–28.81)	(12.19–296.10)	(10.30–482.22)
	% women	1.32	2.10*	0.09***
		(0.64–2.73)	(0.91–4.88)	(0.04–0.21)
ILLNESS LEVEL	Avg. Nr. NCDs	1.12	1.07	0.56***
		(0.90–1.41)	(0.81–1.41)	(0.46–0.69)
	Avg. Nr. Disabilities	0.95	1.12**	0.92
		(0.84–1.07)	(1.01–1.25)	(0.83–1.03)
	Avg. Nr. Symptoms	0.71***	0.73***	0.80**
		(0.60–0.84)	(0.60–0.88)	(0.65–0.99)
	Senior Deaths/1,000	1.07***	1.03***	0.95***
		(1.05–1.08)	(1.01–1.04)	(0.93–0.96)
ENABLING	Rural Characteristics	0.52***	0.9	0.58***
		(0.45–0.59)	(0.78–1.04)	(0.50–0.66)
	Avg. Income	1.06***	1.06***	1.03***
		(1.03–1.10)	(1.04–1.07)	(1.01–1.04)
	% Private H. Insurance	1.56*	8.23***	4.16***
		(1.00–2.46)	(4.76–14.26)	(2.46–7.04)
	% High Utilizers	3.19***	0.54*	0.09***
		(1.67–6.09)	(0.27–1.10)	(0.06–0.14)
	% Preventative exam	1.54	N/A	0.98
		(0.68–3.50)	N/A	(0.34–2.85)
	Hosp. admissions/1,000	1.01***	0.9998	1.00***
		(1.00–1.01)	(0.9996-1.0002)	(1.00–1.00)

Notes: Multi-level generalized latent mixed regression models including random intercept at the area level (subprefecture). Models are weighted by inverse probability of selection. Models include all characteristics at the individual level, plus one of the community-area variables. Estimates are odds ratios, presented with 95% confidence intervals and significance levels (p-value). Outcome: average odds of polypharmacy, measured at the individual level.

Area-level variables derived from the SABE study: average age, percentage of female, average number of chronic diseases, average number of symptoms, average levels of disability, average per capita income, average rate of private insurance, average rate of high care utilizers, and average rate of preventative exams. These variables reflect averages for the population of 60-year olds and over in each of the geographic areas. Mortality among 60-year olds and over, and hospital admissions obtained from the Ministry of Health's Vital Statistics and Health Utilization databases. Percentage of seniors and rural area characteristics obtained from the Brazilian Census.

Table 4.16 displays a comparison between the two full models that we implemented: Model 1 examines the association between polypharmacy and individual characteristics. Model 2 examines the association between polypharmacy and area-level characteristics, controlling for individual factors. Our choice of area-level covariates was based on the investigation presented in Table 15.

The inclusion of area-level factors did not modify the associations that we had estimated with the individual-level regression models. The coefficients from Model 1 vary minimally when the area-level covariates are included, in Model 2.

The models still support the relationships between the area-level factors that we described in Table 15 and polypharmacy. Especially, enabling factors at the community level were associated with higher likelihood of polypharmacy independently of the individual characteristics. Higher income and higher rates of health insurance were associated with increased odds of polypharmacy, and predominance of rural areas was associated with decreased odds of polypharmacy. Similarly, a positive association between mortality of individuals 60 years old and over and polypharmacy, remaining after controlling for all individual and area-level characteristics simultaneously, supported the possibility that illness level factors at the community level may modify individual's likelihood of polypharmacy.

Table 4.16 Full models of the association of individual and area-level characteristics and polypharmacy

	2000		2006		2010	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
Individual-Level						
Predisposing						
Age/ 10yr	1.25 (0.08)***	1.26 (0.08)***	1.05 (0.10)	1.07 (0.09)	1.38 (0.10)***	1.39 (0.10)***
Female	1.37 (0.16)*	1.40 (0.16)**	1.00 (0.18)	0.96 (0.18)	0.85 (0.18)	0.86 (0.18)
Married	1.13 (0.16)	1.13 (0.16)	1.35 (0.16)*	1.36 (0.17)*	0.97 (0.14)	0.97 (0.15)
Smoking	0.67 (0.22)*	0.66 (0.21)*	0.73 (0.34)	0.73 (0.34)	0.83 (0.26)	0.82 (0.26)
Alcohol use	0.94 (0.21)	0.95 (0.21)	0.76 (0.15)*	0.75 (0.16)*	0.80 (0.15)	0.81 (0.15)
Enabling						
P.C. Income/$ 100	1.03 (0.01)***	1.03 (0.01)***	1.01 (0.01)	1.01 (0.01)	1.01 (0.00)*	1.01 (0.00)*
Private h. insurance	1.32 (0.20)	1.33 (0.22)	1.13 (0.16)	1.13 (0.17)	0.85 (0.16)	0.83 (0.19)
High care utlization	1.87 (0.18)***	1.86 (0.18)***	1.72 (0.19)***	1.69 (0.23)**	2.04 (0.18)***	2.03 (0.19)***
Preventative exam	1.17 (0.16)	1.16 (0.16)	1.79 (0.16)***	1.82 (0.17)***	1.13 (0.20)	1.12 (0.20)
Illness Level						
Nr. Chronic Diseases	1.81 (0.07)***	1.82 (0.06)***	2.05 (0.08)***	2.04 (0.08)***	2.26 (0.05)***	2.25 (0.05)***
Nr. Symptoms	1.22 (0.04)***	1.22 (0.05)***	1.13 (0.06)**	1.14 (0.06)**	1.12 (0.05)**	1.11 (0.05)**
Nr. ADLs with Disability	1.17 (0.13)	1.04 (0.03)	1.12 (0.03)***	1.12 (0.03)***	1.03 (0.03)	1.03 (0.03)
Area-Level						
Enabling						
Rural area		0.79 (0.04)***		0.50 (0.06)***		0.80 (0.07)***
Avg. PC. Income /$ 100		1.04 (0.02)*		0.99 (0.01)		1.00 (0.01)
% health insurance		0.93 (0.30)		14.51 (0.35)***		3.51 (0.30)***
% high care utilizers		1.40 (0.27)		1.04 (0.26)		0.21 (0.26)***
Illness Level						
Deaths 60+ /1,000 hab		1.03 (0.00)***		1.05 (0.01)***		0.97 (0.01)***
Model Statistics						
Constant term	0.01 (0.31)***	0.00 (0.36)***	0.01 (0.26)***	0.00 (0.43)***	0.03 (0.25)***	0.15 (0.42)***
N	2126	2126	1350	1350	1309	1309
RE Variance (se)	0.085 (.011)	0.045 (0.009)	0.161 (0.028)	0.218 (0.027)	0.125 (0.028)	0.082 (0.018)

Notes:

Multi-level generalized latent mixed regression models including random intercept at the area level (subprefecture). Models are weighted by inverse probability of selection.

Model 1 includes characteristics at the individual level, identified as: enabling, predisposing, and illness level.

Model 2 includes all individual-level characteristics, plus community characteristics divided as: enabling, illness levels.

Estimates are odds ratios, presented with 95% confidence intervals and significance levels (p-value)

Outcome: odds of polypharmacy, measured at the individual level

Area-level variables: average per capita income, average rate of private insurance, average rate of high care utilizers calculated from the data from the SABE survey, and reflect year-specific averages for the population of 60-year olds and over in each of the geographic areas. Mortality among 60-year olds and over, and rural area characteristics obtained from the Ministry of Health's Vital Statistics database and the Brazilian Census, respectively.

(a) Age calculated in 10-year intervals, centered at age 60.

(b) Reference: not currently married or in a civil union.

(c) Income measured in Brazilian Reais and presented at $100 intervals.

(d) Chronic diseases: self-reported information on ever having been diagnosed with one or more of the following conditions: hypertension, diabetes, heart disease, lung disease, stroke, cancer, psychiatric conditions, joint diseases, or osteoporosis.

(e) Reference: no private health insurance

(f) Self-reported information on having experienced persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo, tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence in the last 12 months.

(g) ADL: activities of daily living. Self-reported information on having difficulty performing one or more of the following activities: walking across a room, getting dressed, bathing, feeding, transferring to/from bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores.

(h) Self-reported information of the number of medical visits in the last 12 months. Moderate-high utilization: more medical visits than the median across all areas in each year. Reference: fewer number of medical visits than the year median.

(i) Self-report of having undergone mammogram (women) or prostate exam (men) in the last 24 months.

(j) Reference: not currently smoking

(k) Reference: no current use of alcohol

4.4.5 Part 5 – Individual and Community-Level Factors Associated with Inappropriate Polypharmacy

We investigated the association between individual and community-level factors inappropriate polypharmacy utilizing the same framework presented for polypharmacy. Table 17 describes the results.

The findings related to inappropriate polypharmacy were largely the same as described in relation to polypharmacy in the previous section. At the individual level, inappropriate polypharmacy was associated with greater health care utilization, including private insurance coverage. Higher health need as indicated by illness levels was also positively associated with inappropriate polypharmacy. The findings from individual-level characteristics were not significantly modified when community characteristics were brought to the model. The community-level associations were also qualitatively similar to those described with polypharmacy. However, there was a general tendency for lower coefficients in this analysis, suggesting that the magnitude of the associations between the multiple factors and inappropriate polypharmacy may be relatively smaller than with polypharmacy.

In the previous section we hypothesized that the effect from higher mortality at the community level and polypharmacy could be due to changes in physician behavior in response to more lethal disease patterns.

Physician prescribing practices may also underlie the associations that we found between higher rates of private health insurance coverage and higher likelihood of inappropriate polypharmacy, both at the individual and at the community level. These associations will be explored in more detailed in the next chapter.

Per capita income was positively associated with the odds of polypharmacy, as was higher prevalence of health insurance among seniors. The estimates indicate that, from two individual with same personal characteristics living in areas that differ only by their prevalence of heath insurance, the individual living in an area where all seniors have health insurance would have five times greater odds (in 2006) and almost four time greater odds of polypharmacy (in 2010) than the individual living in an area where no seniors have health insurance. These findings suggest that the resources at the area level may play a significant role in determining an individual's likelihood of polypharmacy, in excess of an individual's personal resources.

Table 4.17 Individual and community-level factors associated with inappropriate polypharmacy

	2000		2006		2010	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Individual-Level						
Predisposing						
Age/ 10yr	1.12 (0.10)	1.13 (0.10)	1.30 (0.07)***	1.28 (0.08)***	1.22 (0.08)**	1.21 (0.09)**
Female	1.47 (0.15)**	1.53 (0.16)***	1.08 (0.22)	1.07 (0.22)	0.97 (0.23)	0.96 (0.24)
Married	1.30 (0.19)	1.30 (0.19)	1.61 (0.22)**	1.59 (0.22)**	1.05 (0.24)	1.02 (0.24)
Smoking	0.84 (0.25)	0.82 (0.24)	0.99 (0.31)	0.99 (0.31)	0.95 (0.30)	0.93 (0.29)
Alcohol use	1.03 (0.19)	1.01 (0.18)	0.73 (0.25)	0.73 (0.25)	0.77 (0.22)	0.78 (0.22)
Enabling						
P.C. Income/$ 100	1.03 (0.01)***	1.03 (0.00)***	1.01 (0.01)	1.01 (0.01)	1.00 (0.00)	1.00 (0.00)
Private h. insurance	1.31 (0.18)	1.31 (0.20)	1.77 (0.07)***	1.78 (0.08)***	0.77 (0.16)	0.77 (0.17)
High care utlization	2.15 (0.19)***	2.11 (0.19)***	1.19 (0.06)***	1.18 (0.07)**	1.64 (0.19)***	1.68 (0.21)**
Preventative exam	1.13 (0.19)	1.12 (0.19)	1.11 (0.03)***	1.11 (0.03)***	1.02 (0.21)	1.00 (0.21)
Illness Level						
Nr. Chronic Diseases	1.85 (0.06)***	1.88 (0.06)***	0.82 (0.17)	0.81 (0.19)	1.74 (0.06)***	1.73 (0.06)***
Nr. Symptoms	1.15 (0.04)***	1.14 (0.05)***	1.60 (0.17)***	1.62 (0.19)**	1.09 (0.06)	1.08 (0.06)
Nr. ADLs with Disability	1.34 (0.13)**	1.07 (0.03)**	1.46 (0.17)**	1.45 (0.17)**	1.06 (0.03)*	1.06 (0.03)*
Area-Level						
Enabling						
Rural area		0.97 (0.06)		1.05 (0.06)		1.19 (0.09)**
Avg. PC. Income /$ 100		1.10 (0.02)***		1.05 (0.01)***		0.95 (0.00)***
% health insurance		0.54 (0.26)**		3.58 (0.34)***		3.13 (0.26)***
% high care utilizers		9.46 (0.33)***		1.54 (0.20)**		0.31 (0.30)***
Illness Level						
Deaths 60+ /1,000 hab		1.04 (0.01)***		1.04 (0.01)***		0.97 (0.01)***
Model Statistics						
Constant term	0.01 (0.34)***	0.00 (0.43)***	0.01 (0.32)***	0.00 (0.61)***	0.30 (0.47)***	0.05 (0.40)***
N	2126	2126	1350	1350	1309	1309
RE Variance (se)	0.174 (0.034)	0.138 (0.021)	0.224 (0.039)	0.217 (0.029)	0.143 (0.029)	0.171 (0.028)

Notes:

Multi-level generalized latent mixed regression models including random intercept at the area level (subprefecture). Models are weighted by inverse probability of selection.

Model 1 includes characteristics at the individual level, identified as: enabling, predisposing, and illness level.

Model 2 includes all individual-level characteristics, plus community characteristics divided as: enabling, illness levels.
Estimates are odds ratios, presented with 95% confidence intervals and significance levels (p-value)
Outcome: odds of polypharmacy, measured at the individual level
Area-level variables: average per capita income, average rate of private insurance, average rate of high care utilizers calculated from the data from the SABE survey, and reflect year-specific averages for the population of 60-year olds and over in each of the geographic areas. Mortality among 60-year olds and over, and rural area characteristics obtained from the Ministry of Health's Vital Statistics database and the Brazilian Census, respectively.
(a) Age calculated in 10-year intervals, centered at age 60.
(b) Reference: not currently married or in a civil union.
(c) Income measured in Brazilian Reais and presented at $100 intervals.
(d) Chronic diseases: self-reported information on ever having been diagnosed with one or more of the following conditions: hypertension, diabetes, heart disease, lung disease, stroke, cancer, psychiatric conditions, joint diseases, or osteoporosis.
(e) Reference: no private health insurance
(f) Self-reported information on having experienced persistent chest pain, swelling of feet or ankles, dyspnea, dizziness or vertigo, tiredness or fatigue, nausea or vomiting, fecal or urinary incontinence in the last 12 months.
(g) ADL: activities of daily living. Self-reported information on having difficulty performing one or more of the following activities: walking across a room, getting dressed, bathing, feeding, transferring to/from bed, using the toilet, preparing meals, dealing with money, transportation, grocery shopping, using the phone, light household chores, and heavy household chores.
(h) Self-reported information of the number of medical visits in the last 12 months. Moderate-high utilization: more medical visits than the median across all areas in each year. Reference: fewer number of medical visits than the year median.
(i) Self-report of having undergone mammogram (women) or prostate exam (men) in the last 24 months.
(j) Reference: not currently smoking
(k) Reference: no current use of alcohol

4.5 DISCUSSION

The present investigation explored the phenomena of polypharmacy and inappropriate polypharmacy among older adults in Sao Paulo, through an innovative multi-level analytical approach. Combining comprehensive individual- and geographic-level data, we estimated the associations between individual- and area-level factors and the occurrence of polypharmacy and inappropriate polypharmacy. Most importantly, we were able to estimate the association between area-level characteristics and polypharmacy while controlling for individual-level characteristics.

Generally, we found evidence to support that the relationships described in the Andersen framework hold for the use of polypharmacy in the context of Sao Paulo. In addition, our findings suggest that there may also be a role for illness levels and predisposing factors at the community.

We found significant increases, of about two-fold, in the prevalence of polypharmacy and inappropriate polypharmacy over the 10-year period. We found significant geographic variation in the prevalence of polypharmacy and inappropriate polypharmacy across the Sao Paulo sub-prefectures. The variation across areas increased significantly over time.

Most of the variation in the odds of polypharmacy was driven by individual characteristics. Only about 2% of the variation in the odds of polypharmacy across the geographic areas was explained by different propensities at the area level. At the individual level, polypharmacy was mostly associated with higher age, worse health status, and higher health care utilization. Polypharmacy was associated with higher socio-economic status and higher need at the area level.

With the singularities of the Sao Paulo context in mind we can formulate some interpretations to our results: at the individual level we can hypothesize that higher socio-economic status, such as measured by higher income, represents higher ability to pay. Drugs represent a high percentage of medical expenditures in Brazil (Lima-Costa et al., 2003), which could disproportionally harm low-income households. Households with higher incomes may have lower constraints to initiate or to maintain drug utilization, contributing to polypharmacy.

In addition to higher purchasing power, higher socio-economic status at the area level may affect polypharmacy through higher access to care and providers. There is evidence that private services tend to be concentrated in areas with higher socio-economic status (Paulo & Pública, 2011). Even though access to providers is not necessary in order to initiate a drug or to maintain it, higher access to care may increase the likelihood of diagnosing underlying health conditions and may increase the number of new prescriptions. In addition, prescribers in areas with higher incomes may have different preferences and practice patterns than those in areas with lower incomes.

In our study, higher incomes at the individual level had low association with polypharmacy. We believe that this may be because income may be an imperfect metric of socio-economic status for the senior population. Persons 60 years old and over may be less likely to have formal employment, or they may rely on family members for

their financial support. In these cases, seniors may report zero or minimal personal income.[16] Many of those who have an income may be retired persons reporting on their income from pensions. Because there is a cap on public pensions in Brazil, income from pensions may possibly flatten out differences that may have been present before retirement.

We believe that, in our study population, the rates of private health insurance coverage may be a better marker of area-level socio-economic status than average income levels. Because the cost of private health insurance is high, having private health insurance may be a stronger marker of higher socio-economic status and ability to pay than income. A senior citizen who can afford private health insurance is more likely to be able to afford pharmaceuticals than a person who cannot afford or who chooses not to purchase private health insurance. Or, a senior citizen whose family can finance their private health insurance is more likely to have their drugs financed by family members as well.

From the literature from high-income settings there is evidence that provider preferences explain much of the geographic variations of health care utilization, more than differences in demand or population health needs (Cutler et al., 2013; Fisher et al., 2003b). This could also be the case in Brazil. Provider preferences could be a significant underlying driver of the association that we found between higher private health insurance rates at the area level and polypharmacy. Provider practices may not only vary across geographic areas but also across time. Prescription practices, especially differences between private and public health providers, should be further studied and better understood.

Higher age and higher rates of chronic diseases at the area level may play a role in polypharmacy by modifying the demand for treatments. Because drugs can be purchased over the counter, drug utilization in Brazil may be sensitive to individual preferences shaped by cultural and social expectations. For example, a senior individual who lives in an area where more people are likely to take drugs because they are older or sicker could be influenced to accept, or even expect, the possibility of polypharmacy more easily. In our study we did identify a positive association between polypharmacy and older ages at the community level. However, we identified a negative association with area-level rates of chronic conditions.

[16] The SABE survey questionnaire had very broad questions covering multiple different sources of income (such as remittances, rent, investments and others). However, the questions pertained to the individual being interviewed, and not to the family's main breadwinner.

It is unclear why higher rates of mortality in a community could lead to higher likelihood of polypharmacy and inappropriate polypharmacy. When we compare this association to metrics of disease morbidity, we find a negative association with polypharmacy, especially with levels of chronic diseases, symptoms, and disability levels. We hypothesize that providers may respond differently to rates of morbidity and mortality in their communities.

There may be underlying factors that determine both higher rates of polypharmacy and higher mortality, or worse health status – for example, area-level patterns of exposures, especially those acting throughout the life course (such as education, lifelong occupation, and lifelong socio-economic status) that may predispose to higher occurrence of both disease and morbidity, and lower likelihood of accessing, affording, or accepting pharmaceutical treatments.

4.6 LIMITATIONS

The main limitation of this study is that our data source, the SABE survey, was not designed to address questions of geographic variation. The sample size was calculated to represent the population of the entire city of Sao Paulo in each year. The study was not powered to look at differences across areas. Also, the number of geographic areas contributing level-2 information to our analyses in each year was small: 30 sub-prefectures. These factors may underlie some of our findings such as very large confidence intervals and changes in direction of the associations across the survey waves.

The possibility of low power to detect differences at the area level could have biased our results towards the null hypothesis (type 1 error). Also, some characteristics, such as the prevalence of health insurance and the presence of private health services, may be correlated at the area level; therefore, there might not have been enough covariance patterns across the areas, and some analyses may have relied on extrapolation. This could have biased our results. Some approaches to mitigate this possibility, such as propensity scores and matching methods, might be explored in futures studies.

Our choice of sub-prefectures as the level -2 unit of analysis was motivated by the administrative structure of public services, specifically of the public health system, in Sao Paulo. This choice was not in line with the majority of the literature on geographic variation of health care utilization. The literature has traditionally utilized approaches such as hospital referral regions (HRRs), hospital service areas (HSAs) and metropolitan statistical areas (MSAs).

It makes sense to use sub-prefectures as the unit of analysis in Sao Paulo since they correspond to administrative divisions involved in health care provision. At the present moment, alternative units of analysis such as HRRs and HSAs have not been developed in Latin America. The main advantage of using administrative divisions as unit of analyses is that they are easier to match with health systems and other population and community characteristics. Administrative divisions, however, may not reflect actual utilization patterns, since some of the units may lack a hospital or a pharmacy, for example.

We assumed that the selected individuals who participated in the survey in each area were representative of the population of seniors living in that area. This assumption is does not necessarily hold, because the sampling process was not performed with the goal of representing the sub-prefectures. Rather, the SABE study sampling was performed with the goal of representing the population of 60 year-olds and over across Sao Paulo. Because sub-prefectures play an important role in the management of the public health system, future studies should consider stratifying their sampling processes by sub-prefecture, to ensure representativeness at the sub-prefecture level.

Our multi-level models assume that controlling for sub-prefecture membership completely accounts for the correlations that may exist between individuals living in the same sub-prefecture. The assumption is that, when subprefecture membership is accounted for, individuals are independent from each other. For this assumption to hold, however, there should be no reverse causation – i.e., people with greater propensity for polypharmacy would not differentially select to live in areas of high income, or higher health insurance coverage for example. This possibility seems unlikely, but it could be explored in future studies.

Also, the assumption of residual confounding – i.e., that there are no characteristics missing in our models that affect both the outcome and the main covariates – needs to hold in order to support our interpretation of our results. We believe that this possibility should be further examined. We did not cover all the relevant aspects of access to care in the geographic areas. There may be other health system factors – such as availability and type of service – that could distort our results if they remain unidentified.

We provide a more detailed discussion of other relevant aspects of our methodology – especially the possible limitations – in the final discussion, in Chapter 6.

4.7 CONCLUSION

The present study implemented an innovative approach – a multi-level investigation – to address the occurrence of polypharmacy and inappropriate polypharmacy in Sao Paulo, Brazil.

Multi-level investigations are highly desirable as the phenomenon of polypharmacy is multi-level by nature (Phillips, Morrison, Andersen, & Aday, 1998). Our empirical results corroborate that. We utilized a conceptual framework that has been historically employed in investigations of other forms of health care utilization, including polypharmacy (Aparasu, Mort, & Brandt, 2005). However, this is the first time that the behavioral model framework is employed in a multi-level investigation of polypharmacy. The fact that we were able to utilize information from a representative sample of individuals living in one of the major cities of Latin America is presents a significant contribution to the field. In addition, we believe that our findings can inform further modifications to this framework as we found evidence of roles of illness level factors at the community level independently of the individual level illness levels.

We found that individual characteristics such as older age, worse health, and higher use of services are the factors most strongly associated with higher odds of polypharmacy in Sao Paulo. We found that geographic factors explain only about 2% in the variation in the odds of polypharmacy. However, geographic factors such as higher mortality and higher socio-economic status at the community level were independently associated with higher odds of polypharmacy, and those associations remained after controlling for individual factors.

Higher income and higher rates of private insurance in the community were more strongly associated with polypharmacy than income and insurance status at the individual level, indicating that area-level resources may be more important than the person's financial resources in determining their odds of polypharmacy.

Our study does not elucidate causal pathways through which these factors may influence the odds of polypharmacy. However, it indicated that further investigations of factors such as provider characteristics, availability and quality of care at the area level, should be conducted. These hypotheses should be further explored, as they could help elucidate potential policy targets to improve elderly care and increase efficiency in the use of resources in settings like Sao Paulo.

5. CHAPTER V: HEALTH SYSTEMS FACTORS ASSOCIATED WITH POLYPHARMACY IN OLDER ADULTS: A MULTI-LEVEL ANALYSIS

ABSTRACT

Background: The growing use of pharmaceuticals worldwide may be a response to a greater prevalence of chronic diseases. However, not all drug utilization is driven by need. Polypharmacy that is not driven by health need is undesirable, because it exposes individuals to higher risk and higher spending, without corresponding health gains.

Aims: In this study we analyze the association between polypharmacy and health systems characteristics, controlling for individual and community-level factors; and quantifying the contribution from individual, community, and health systems factors to explain geographic variation in polypharmacy.

Method: We combined data from older adults living across multiple sub-prefectures of Sao Paulo, Brazil, with health systems information on each of the sub-prefectures. We implemented multi-level generalized latent mixed models to identify the associations between health systems characteristics and polypharmacy while controlling for individual and other area-level characteristics.

Results: We found that health systems factors such as higher availability of private pharmacies, presence of hospitals, higher private health insurance coverage and higher enrollment in the family health program, at the area level, are positively associated with polypharmacy, even when controlling for multiple individual factors. However, they explain only a small portion of the variation in polypharmacy across individuals. We found that patient characteristics accounted for 23-26% of the geographic variation in drug use; while health systems and community-level factors accounted for only 0.2-0.6% of the residual variation.

Discussion: Our findings support the possibility that polypharmacy may exhibit a pattern of supply-sensitive care in Sao Paulo. Polypharmacy was associated to health system characteristics that are linked to availability

and complexity of care. Our findings suggest that doctor's visits in the public health system, and interactions with private pharmacies, should be explored as potential policy targets to mitigate polypharmacy, as they may provide opportunities to drug revision and discontinuation. Further aspects of the health system, such as providers' preferences and prescribing practices, and differences across the public and private systems in Brazil, should be examined in further studies.

5.1 INTRODUCTION

5.1.1 Policy Problem: Supply-Sensitive Utilization of Polypharmacy

Pharmaceuticals have long been central to many different medical treatments. Some breakthroughs in disease treatment have come from pharmaceutical discovery. As chronic diseases have become more prevalent, pharmaceuticals are being used not only to treat, but also to prevent chronic conditions and their complications. Often pharmaceutical utilization that meets health needs is considered "effective care" (Fisher & Wennberg, 2003) and is highly desirable, as it tends to have greater benefit than risk. However, this is not always the case.

Not all drug utilization reflects effective care. Pharmaceutical utilization driven by factors other than health need is undesirable, because it exposes individuals to higher risk and higher spending, without corresponding health gains. Polypharmacy, the use of multiple pharmaceuticals per day, is a situation in which drug risks may exceed the clinical benefits. Polypharmacy may be clinically appropriate; however, it may also be a response to the preferences of patients, who often equate health care to the prescription of pharmaceuticals (Busfield, 2010). Polypharmacy may also reflect the preferences and practices of health providers, such as a tendency to prescribe pharmaceuticals to manage symptoms and signs that are not pathological, but that are part of the normal life cycle and aging process (Williams et al., 2011). It could also be based on clinical need if the person has multiple diseases.

Polypharmacy has been associated with increased risk of drug-related problems such as adverse effects and drug interactions. The levels of risk tend to increase as the number of drugs in a pharmaceutical regimen increases. There is no consensus, however, among clinical communities, as to whether all cases of polypharmacy are necessarily and equally risky,[17] and as to how many drugs are considered too many. In general, a definition of five or more drugs per day is accepted, because regimens above this threshold have been associated with increased risk of frailty, cognitive impairment, and mortality (Gnjidic et al., 2012).

[17] We present an analysis of the risk of polypharmacy among our study population in Chapter III.

In this chapter, we examine the possibility that polypharmacy may correlate with differences in the availability of health services in a community. We have previously demonstrated that other community characteristics – urban location and higher socio-economic status, for example – are associated with higher likelihood of polypharmacy independently from individual characteristics such as level of income and level of health need.[18] Situations of therapeutic uncertainty like polypharmacy, where there is no consensus as of which levels of utilization are optimal, tend to be influenced by the supply of health resources. This is sometimes called "supply-sensitive care" (Fisher & Wennberg, 2003).

We focus our investigation on older adults living in communities across the city of Sao Paulo, Brazil. Older adults they tend to utilize more drugs than the rest of the population, especially polypharmacy. These individuals tend to be more vulnerable to drug-related risks and tend to spend greater portions of their incomes on drugs.

Our target audience is policy-makers who may want to protect older adults from unnecessary polypharmacy and its associated risks and financial burden. Because public health resources are often used to provide or subsidize pharmaceutical treatments for the older adult population in Brazil, the management of polypharmacy also poses questions about appropriate allocation of public health resources in that context.

5.1.2 Pharmaceutical Utilization Among Sao Paulo Older Adults

The population of Sao Paulo is rapidly aging (A. Palloni et al., 2002). There is evidence that pharmaceutical use is frequent, and that drug risk is a potential problem among the Sao Paulo older adult population. It is estimated that about one in five older adults in Sao Paulo is exposed to at least one potential drug-drug interaction, with various levels of clinical significance (Secoli et al., 2010).

Our previous investigation found that polypharmacy doubled, from 16% to about 38%, among the Sao Paulo older adult population between 2000 and 2010. As the exposure to polypharmacy grew, so did the possibility of

[18] We present an analysis of the association between community characteristics and polypharmacy among our study population in Chapter IV.

drug-related risk associated with it. We estimated that inappropriate polypharmacy, the use of five or more drugs a day with at least one drug risk criterion, grew from about 13% to 23% in the same period (see Chapter 3).

Polypharmacy may be associated with inadequate clinical monitoring. When an individual is diagnosed with a drug-related condition such as drug-induced Parkinsonism, the lack of clinical follow-up may prevent the offending drug from being discontinued, with some patients remaining on inappropriate treatments for periods of up to a year (Barbosa et al., 2006).

Access to medicines in Sao Paulo occurs through two main mechanisms: drugs can be purchased out-of-pocket in the private market, a situation that often dispenses with the need of a formal medical prescription; or drugs can be obtained free of cost from government pharmacies. Public distribution of drugs is limited to a national formulary, and it requires medical prescriptions that must be current and must be issued by a public health service (Secretaria de Políticas de Saúde, 2000).

Private health insurance plans do not cover drugs for outpatient use in Brazil. However, private insurance allows for faster access to medical visits and for access to networks of private providers, which is otherwise only accessible out-of-pocket. Whereas requirements to access medical services (such as pre-authorization) vary by insurance plan, in the public health system there is a hierarchy prioritizing primary care. Primary care clinics and providers are the gateway to the system, which can only be bypassed by urgent care, such as in Emergency departments, for example (Paulo & Pública, 2011).

There is a great overlap between higher socio-economic status and private health insurance coverage in Sao Paulo. About 70% of residents of predominantly rich areas have private health insurance, whereas a maximum of 30% of people have private health insurance in predominantly poor areas (Paulo & Pública, 2011). The distribution of private health services greatly overlaps with areas of higher socio-economic status and greater private health insurance coverage in the city. This is especially true for complex services such as hospitals and tertiary care centers.

The distribution of public health services does not exhibit the same pattern. The allocation of public health services has been at least to some extent intended to cover underserved areas with greater population health needs (Paulo & Pública, 2011). Of note, the public health system provides each area with a number of family health teams (FHT). The FHT are part of the Family Health Program, which provides periodic home visits to families in the catchment area of a primary care clinic. The FHT are composed by a minimum of one doctor, one nurse, and one community health worker. The FHT visits provide primary care interventions such as blood pressure checks, weight measurement and others, including review of pharmaceutical treatments and, in some cases, delivery of medicines (Paulo & Pública, 2011).

Most individuals who live in predominantly poor areas or in areas transitioning into middle class rely exclusively on the public health system to obtain their care. About half of the Sao Paulo population depends exclusively on the public health system to obtain care. This represents higher rates of private insurance coverage than the average for Brazil, which is about 25% (Viacava et al., 2005).

5.1.3 Administrative Divisions of the City of Sao Paulo

Sao Paulo is unique in terms of its country-size proportions. Its population of about 12 million people is larger than countries like Greece and Bolivia (Factbook, 2010). The city is divided into 31 administrative areas called sub-prefectures, who are responsible for managing local public services, including the delivery of health services on the public health system.

Socio-economic status and housing conditions vary significantly across the 31 Sao Paulo sub-prefectures (Table 5.1). While the more centrally located areas are densely populated and heavily urban, there are peripheral areas that have almost rural characteristics. About a third of the Sao Paulo population lives in predominantly poor areas; a third in areas transitioning into the middle class; and a third in predominantly middle class areas; a minority (about 10%) lives in predominantly rich areas (Paulo & Pública, 2011).

Table 5.1 Socio-Demographic Characteristics of the Sao Paulo Sub-Prefectures.

Subprefecture	Area (1,000 km^2)	Total pop	% 60+	% illiterate	% sub-optimal housing	Avg. income	Nr. Hospitals	Nr. 1ary care clinics
Aricanduva/Formosa/Carrão	21.50	266,838	13.22%	5.38%	9.72	814.19	3	9
Butantã	56.10	377,576	9.18%	6.68%	9.63	2042.10	9	14
Campo Limpo	36.70	505,969	4.95%	9.85%	14.73	1208.88	1	22
Capela do Socorro	134.20	563,922	5.15%	9.54%	16.55	876.03	3	15
Casa Verde/ Cachoeirinha	26.70	313,323	9.70%	7.31%	8.71	1929.41	3	12
Cidade Ademar	30.70	370,797	5.94%	9.60%	11.67	932.35	0	17
Cidade Tiradentes	15.00	190,657	3.31%	9.90%	1.11	793.21	0	12
Ermelino Matarazzo	15.10	204,951	8.31%	7.26%	7.11	1294.65	4	11
Freguesia do Ó/Brasilandia	31.50	392,251	7.74%	8.57%	8.45	1030.76	1	15
Guaianases	17.80	256,319	4.78%	10.88%	0.82	591.61	2	15
Ipiranga	37.50	429,235	11.74%	6.20%	3.99	3363.73	8	17
Itaim Paulista	21.70	359,215	5.32%	9.99%	6.04	1525.29	2	16
Itaquera	54.30	489,502	6.37%	7.74%	13.98	2640.48	4	21
Jabaquara	14.10	214,095	10.15%	6.67%	7.99	510.80	6	5
Jaçanã/Trem	64.10	255,612	8.64%	8.14%	13.09	985.12	4	11
Lapa	40.10	270,656	15.73%	3.91%	0.92	1352.66	8	10
M'Boi Mirim	62.10	484,966	4.47%	10.24%	1.61	543.95	2	32
Mooca	35.20	308,161	17.64%	3.77%	2.83	1380.77	14	11
Parelheiros	353.50	111,240	4.01%	11.94%	–	999.03	0	8
Penha	42.80	475,879	11.45%	5.74%	3.72	949.46	3	18
Perus	57.20	109,116	4.64%	10.09%	–	2667.29	0	6
Pinheiros	31.70	272,574	18.99%	1.81%	5.76	1817.78	12	6
Pirituba	54.70	390,530	7.77%	7.07%	9.57	825.82	5	17
Santana/Tucuruvi	34.70	327,135	14.01%	3.73%	2.69	2198.82	10	7
Santo Amaro	37.50	218,558	14.10%	3.36%	2.60	2753.12	10	6
São Mateus	45.80	381,718	5.64%	9.29%	3.42	1599.22	4	22
São Miguel	24.30	378,438	6.23%	10.20%	13.26	1496.74	5	14
Sé	26.20	373,914	15.71%	3.40%	3.06	1649.14	30	7
Vila Maria/ Vila Guilherme	26.40	304,393	12.01%	7.13%	7.44	1740.71	5	13
Vila Mariana	26.50	313,036	16.76%	2.04%	1.05	732.57	29	7
VilaPrudente/Sapopemba	33.30	523,676	9.52%	7.26%	4.40	1433.44	5	23

* Hospitals and Public Clinics data from 2006; else data from 2000. Source: Brazilian Census and CE info.

5.1.4 Evidence Linking Polypharmacy to Health Systems Characteristics

Studies of health care utilization and health spending have demonstrated that not all utilization is driven by greater health need. The main analytical framework demonstrating this is the analysis of small area variations in health care utilization, or simply, geographic variation studies (J. Wennberg & Gittelsohn, 1973). The concept behind such analyses is that, once the characteristics of the individuals are accounted for, variations may correlate to characteristics occurring at the area-level, such as the supply of health services.

Individual-level characteristics such as health status tend to account for a small proportion of the variation in health care utilization observed across geographic areas: among older adults in the United States health status explained less than a third (29%) of area-level differences in total health spending (Zuckerman et al., 2010).

Another study found that patient characteristics such as income and health explained 12% of the variation in spending while patient preferences explained an additional 5% (Baker et al., 2014).

Supply-side characteristics have been demonstrated to explain the majority of the variation in health care utilization (Cutler et al., 2013; Medicine, 2013; J. E. Wennberg, 2014; J. Wennberg & Gittelsohn, 1973). In the case of pharmaceuticals, supply-side characteristics explained up to 50-60% of the variation in use (King & Essick, 2013).

In the case of polypharmacy, the peer-reviewed literature suggests that some of the supply-side factors that could influence its utilization are:

- Therapeutic guidelines and medical evidence may not provide a consensus as to what an optimal level of utilization would be, allowing providers to interpret and apply them with different interpretations (Cutler et al., 2013)
- Physicians may have different preferences and beliefs regarding pharmaceutical treatments, motivating them to be more "aggressive" in their prescribing practices than others (Cutler et al., 2013)
- Marketing practices by the pharmaceutical industry may target geographic areas with different intensity, influencing provider behavior (de Bakker, Coffie, Heerdink, van Dijk, & Groenewegen, 2007; King & Essick, 2013)
- Prescribing preferences may vary by physician specialty and may reflect the "provider mix" of specialties in a given area (Fisher & Wennberg, 2003; J. Wennberg & Gittelsohn, 1973)
- Higher rates of insurance coverage in an area may lead to higher access to physicians, facilitating the prescription of drugs (King & Essick, 2013)
- Higher availability of services and doctors may lead to greater number of prescriptions (Fisher, 2000)

The relative importance of supply- and demand- factors in explaining variation in health care utilization varies across countries and settings. It has been consistently demonstrated, however, that is no correlation between levels of health services utilization and health outcomes (Medicine, 2013). In addition, there tends to be no correlation between the availability of health services and underlying population health needs (J. Wennberg & Gittelsohn, 1973)

So far, no geographic variation analyses of health care utilization have been conducted in the Sao Paulo context. Such analyses could provide important insights to policy-makers, especially those who are in charge of allocating health resources across the multiple geographic areas of the city.

5.2 AIMS

The main aim of this study is to identify supply-side health systems factors associated with polypharmacy in the Sao Paulo older adult population. Specifically, we aim to: analyze the association between polypharmacy and health systems characteristics, controlling for individual and community-level factors; and to quantify the extent to which health systems factors contribute to explaining geographic variations in polypharmacy in addition to the variation explained by individual- and community-level factors.

5.3 HYPOTHESES

If polypharmacy were utilized mainly in response to underlying health needs, such as greater number of chronic diseases, this would be associated with "effective care" (Fisher & Wennberg, 2003). If “effective care’ was responsible for most of the utilization differences then we would expect that the occurrence of polypharmacy would be mostly explained by the presence and number of chronic diseases, and the level of symptoms and of disability, at the individual level.

If polypharmacy were utilized mainly in response to the availability of services and providers at the community level, this would represent "supply-sensitive care" (Fisher & Wennberg, 2003). We would expect that the characteristics at the individual level would less of the variation in the use of polypharmacy; instead, we would expect polypharmacy to be correlated with characteristics at the health system level, such as the availability of health services and physicians in a given area.

A third case would be if polypharmacy reflected trade-offs in care subject to preferences of patients- reflecting "preference-sensitive care" (Fisher & Wennberg, 2003). That case might be undistinguishable from either of the cases above, given the information that we have. Patients often delegate decisions to doctors and preference-sensitive care may behave like supply-sensitive care in some cases.

5.4 METHODS

5.4.1 Data

We combined individual information from a household survey of older adults living in Sao Paulo with information on health system characteristics of the corresponding areas where individuals lived obtained from publicly available government databases in Sao Paulo.

The survey – the SABE study (Health, Wellbeing and Aging) – examined older adults 60 years old and over living in the community in Sao Paulo in the years 2000, 2006, and 2010. The survey had a census-based multi-stage sampling process that is described in greater detail in Chapter II and in other academic publications (Lebrao & Duarte, 2003; A. Palloni et al., 2002). When weighted by the inverse probability of selection the SABE sample was representative of the population of non-institutionalized older adults in Sao Paulo in each of the survey years.

The survey collected extensive health, demographic and socio-economic information of participants, including the use of medicines. The survey recorded information on all types of pharmaceutical products, including nutritional supplements, herbal and homeopathic medicines, and compounded substances. Because of the coding used for data entry, which followed the World Health Organization's Anatomical Therapeutic Chemical classification (WHO-ATC), we were only able to examine prescription and over-the-counter drugs in our analyses. We defined polypharmacy as the use of five or more prescription or over-the-counter drugs per day. Chapter II provides a complete description of the variables collected in the SABE study.

We collected information on health systems variables from several publicly available government databases from the Health Secretariat and Urban Development Secretariat of the Sao Paulo Municipality (*Secretaria Municipal de Saúde e Secretaria Municipal de Desenvolvimento Urbano*), the Sao Paulo State Data Analysis Foundation *(SEADE: Fundação Sistema Estadual de Análise de Dados*), and the Brazilian National Institute for Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística*), which conducts the Brazilian Census. Most of the data obtained from the Sao Paulo offices was linked to the DATASUS online database from the Brazilian Ministry of Health.

The unit of the geographic variation characteristics was the sub-prefecture level. All information obtained from the official government sources was provided either at the level of sub-prefecture (higher level) or at the level of district (lower level). There is a strict correspondence between district and sub-prefecture. Each of the sub-prefectures contains from one to seven districts, which are fixed. When we were only able to obtain district-level data, we aggregated it at the sub-prefecture level. We linked all individual information with geographic area information using the sub-prefecture where the individuals lived.

Table 5.2 displays the health systems indicators collected, the years available, and the sources. We transformed all count variables ("nr. of physicians", etc.) in numbers per 100,000 inhabitants, using information from the Brazilian Census.

As can be seen from the Table 5.2, some community and health systems characteristics were not available for the years corresponding to the SABE study. When there was no information, we did not include the data on our analyses. The only exception was the availability of private pharmacies. We could not obtain historical information on number of private pharmacies per area. The licensing of private pharmacies is performed simultaneously by all sub-prefectures, plus the Sao Paulo main municipal administration, and there was not a unified list that was available for reference. We obtained the information for the year 2016 from a commercial online search tool. We aggregated information by neighborhoods to obtain the sub-prefecture data. The geographic limits of neighborhoods are less precise than districts. The correspondence between neighborhoods and sub-prefectures can be imprecise, because there are a few neighborhoods that belong to two different sub-prefectures. We expected that would be significant measurement error in this indicator, because of the year difference, the non-official source, and the imprecision of the geographic limits of neighborhoods. In order to

minimize the impact of these limitations, we calculated quintiles of concentrations of private pharmacies per area, and we assumed that an area belonged to the same quintile in 2000, 2006, and 2010, as it belonged in 2016. As a data quality check, we used information on public-private pharmacies, a short-lived government program, which we had from 2013; we compared the private pharmacy quintiles against the quintiles of the public-private pharmacies, with significant overlap.

In the case where the information was available for a different year than those of the SABE study, we proceeded in a case-by-case basis with each of the variables. The numbers of doctors were only available starting in 2008. Even though this year did not correspond to the SABE study (2008 versus 2006), we assumed it was constant and so we used the 2008 information in our analyses. We did not use any information for 2000. We used the information on percentage of C-sections and percentage of pregnancies with full antenatal care from 2007 as a proxy for 2006, and we did not use any information in 2000. Lastly, the information on hospital admissions for seniors was available for 2003 but not for 2000. We assumed constant but we used this information only in the sensitivity analyses.

Table 5.2 Health Systems Characteristics – Data Availability and Sources

Indicator	Year				Source
Reference Year	**2000**	**2006**	**2010**	**2010**	
Health Professionals[1]					
Total nr. Physicians		2008	2010		CE info database
Nr. Generalists		2008	2010		CE info online database
Nr. Geriatricians		2008	2010		CE info online database
Nr. Specialists		2008	2010		CE info online database
Nr. Pharmacists		2006	2010		CE info online database
Health Facilities					
Nr. Primary care clinics[1]	2000	2006	2010		Infocidade online database
Nr. Pharmacies[2]				2016	Apontador.com
Nr. Hospitals[3]	2000	2006	2010		CE info online database
Nr. Hospital beds[3]	2000	2006	2010		CE info online database
Health Services Utilization[1]					
Nr. enrolled in the FHP[4]		2006	2010		CE info online database
Total Nr. Hospitalizations	2003	2006	2010		CE info online database
Nr. Primary care visits			2010		SEADE online database
Nr. Specialized care visits			2010		SEADE online database
Nr. Urgent care visits			2010		SEADE online database
% full antenatal care		2007	2010		SEADE online database
% deliveries via c-section		2007	2010		SEADE online database

Notes: [1]Public health system only. [2]Private health System only. [3] Available for both public and private health systems. [4]Family health program. All count variables ("Nr. Of physicians", etc.), were transformed in numbers per 100,000 inhabitants using information from the Brazilian Census. IBGE: Brazilian National Institute for Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística*), SEADE: Sao Paulo State Data Analysis Foundation (*Fundação Sistema Estadual de Análise de Dados*), Infocidade: information portal of the Urban Development Secretariat of the Sao Paulo Municipality (*Secretaria Municipal de Desenvolvimento Urbano*).

In addition to the health systems characteristics, we also collected the rural/urban profile for each area from the Brazilian Census. Because Census information was only available for 2006 and 2010, we interpolated the rural area indicator for 2006 assuming that areas with same rural/urban status in 2000 and 2010 were the same in 2006 (see more details in Chapter 4).

We also calculated some of the area-level characteristics by aggregating information from the SABE participants at the sub-prefecture level. The area-level information utilized in this analysis that we obtained from

the SABE study is displayed in Table 5.3. Of note, this information refers only to the population age 60 years and over.

Table 5.3 Area-level information obtained from the SABE study

Socio-Economic Status	
Income	Average income in Brazilian Reais (R$)
Health Insurance	% of population with private health insurance
Health Utilization	
Preventative exam	% of the population who underwent a preventative exam in the last 24 months (women: mammogram; men: prostate exam).
Immunization	% of the population who received influzenza or pneumonia vaccination in the last 12 months.

5.4.2 Conceptual Framework

We draw from the conceptual framework of Societal and Individual Determinants of Medical Care Utilization developed by Andersen & Newman (Figure 5.1) (R. Andersen & Newman, 1973). In our study the main outcome of interest – "health service utilization" – is the use of polypharmacy.

Andersen and Newman's framework envisioned health services utilization as the result of a "sequence of conditions". At the individual level, the framework divided these conditions as: predisposing conditions ("the predisposition of the individual to use services"), enabling conditions (the individual's "ability to secure services"), and illness level (the diagnoses, level of symptoms and disability perceived by the individual or ascertained by the health provider). We modified this framework to include predisposing, enabling, and illness levels factors at the community level as well (Figure 5.2). We addressed the individual- and the community-level predisposing, enabling, and illness levels factors in our previous analysis (Chapter 4). We allowed community factors to have an independent impact with polypharmacy, when controlling for individual characteristics. This is displayed in the model in the form of a solid arrow (direct effect – we could measure this) plus a dashed arrow (indirect effect – we did not measure this).

In the current analysis we focus on a broader level, in which the Andersen model identified societal and health system's determinants of health utilization. Similarly to the community determinants, the model assumed that societal and health systems determinants affected service utilization only via individual-level characteristics. The possibility that societal and health systems factors might directly affect health services utilization was not included in the model. We assumed that health system's factors had an independent impact with polypharmacy when controlling for individual and community characteristics. We adapted the conceptual framework to identify that effect (solid arrows – Figure 5.2).

We are interested in estimating the direct effect of health system determinants with polypharmacy. We assume that societal determinants (technology and norms) are constant across areas. Technology represents drugs - the drugs available in the private market, the drugs included in government formularies – as well as their prices. Norms represent legislation and regulation establishing the rules for drug prescription, distribution and commercialization. Because our sample comes from one single city, it is highly unlikely that technology and norms would vary significantly across the different areas. For the most part drug regulation and legislation are established at the national level in Brazil. Only certain governmental formularies might be defined by states and cities; still, the formularies would be the same across all sub-prefectures. Still, it would be possible that stock-outs of government formulary drugs might affect some areas more than others. This might occur because of difficulties in transportation, logistics, or because of differences in administrative capacity in each of the areas. We cannot examine this possibility, however. A proxy for the availability of drugs may be area-level income since there is often better access to drugs in more affluent areas.

Figure 5.1 Andersen & Newman's societal and individual determinants of medical care utilization – Conceptual framework

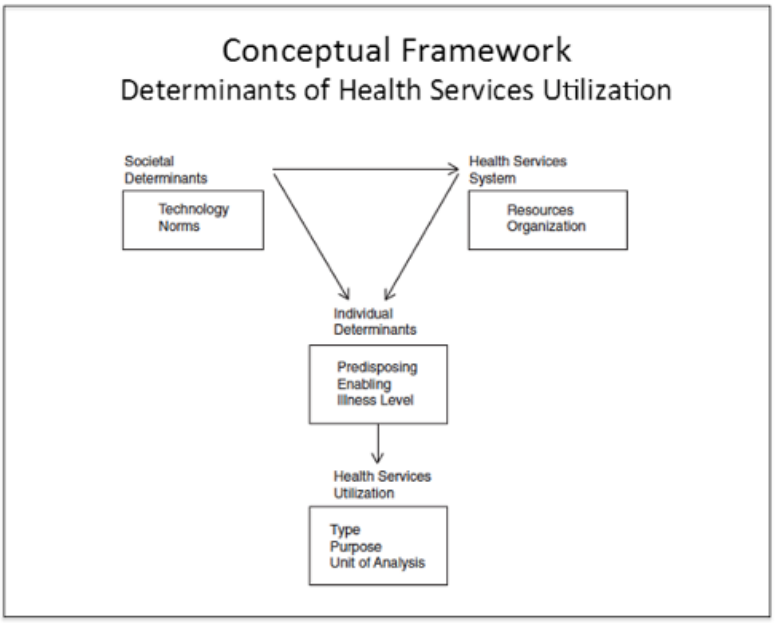
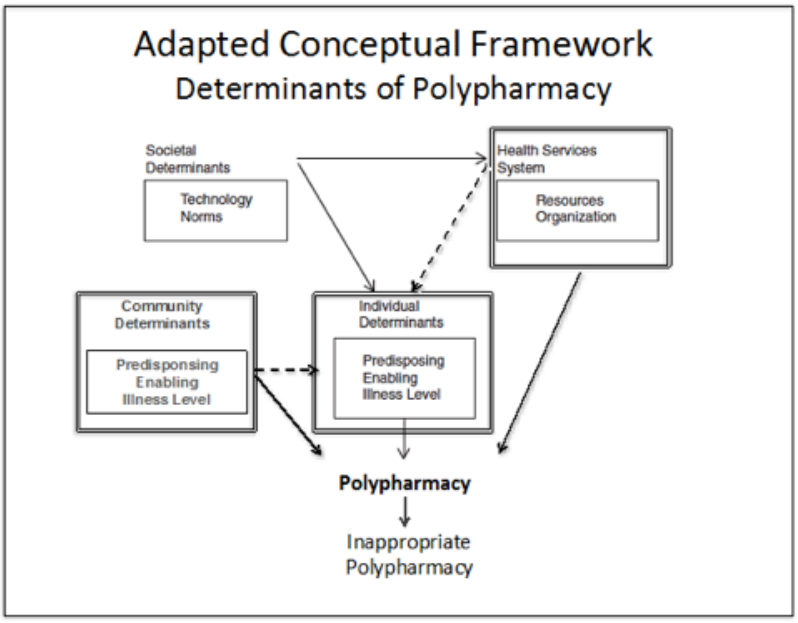


Figure 5.2 Adapted conceptual framework demonstrating community and health services system determinants used in this paper



5.4.3 Analytical Model

We model the log odds of polypharmacy using a multi-level generalized latent mixed model, as follows:

$Log\ [Pr(Y_{ij}=1)/\ Pr(Y_{ij}=0)]=\beta_{0i} + \beta_1 Individual_{ij} + \beta_2 Community_i + \beta_3 Health\ Sys_i$

Where:

- $Log\ [Pr(Y_{ij}=1)/\ Pr(Y_{ij}=0)]$ is the log odds of polypharmacy for subject *j* living in area *i*;
- $\beta_{0i,}$ which can be decomposed as $\beta_{0i} = \beta_0 + b_{0i,}$ is a random intercept that represents the baseline propensity for polypharmacy in each geographic area;
- $Individual_{ij}$ is the vector of predisposing, enabling, and illness level characteristics of subject *j* living in area *i;*
- $Community_i$ is a vector enabling and illness level characteristics of area *i*;
- $HealthSys_i$ is a vector of health systems characteristics of area *i*;
- $\beta_{1,}$ β_2 and β_3 represent log odds ratios for a change in the response variable associated with a 1-unit change in each covariate, holding all others constant;

Assumptions:[19]

We assume that there is a latent (unobserved) continuous response that represents the probability of the observed outcome (polypharmacy or no polypharmacy) for each subject *j* living in area *i*. A positive outcome (polypharmacy) will be observed when the individual's underlying latent variable is greater than zero and a negative outcome (no polypharmacy) will be observed when the individual's underlying latent variable is equal to or lower than zero.

We assume that there is a baseline propensity for a positive outcome (polypharmacy) that varies across areas. The baseline propensity of each area is captured by its random intercept $b_{0i.}$ Differences in the area-specific

[19] For a full set of assumptions see Chapter 4.

baseline propensity for polypharmacy are a result of differences in both measured and unmeasured characteristics of each area.

The model assumes that the propensity for polypharmacy for individuals *j* and *k* living in the same area is correlated. The model assumes that responses are independent once the baseline propensity for polypharmacy of an area (captured by the area-specific random intercept b_{0i}) is taken into account.

The coefficients from the multilevel model represent effects within a given geographic area. In the multilevel model there is a different baseline propensity for polypharmacy in each geographic area. This baseline propensity must be taken into consideration when interpreting the fixed effects from the various covariates in the multilevel model. In the multilevel model a coefficient represents the expected change in the log odds of polypharmacy associated with a one-unit change in a given covariate (holding all other covariates constant) for an individual living in an average area.

5.4.4 Implementation

We ran a series of descriptive analyses in order to describe the levels of individual and geographic characteristics in each of the survey waves. We used inverse probability weighting in order to reconstruct the individual information of the non-institutionalized population of 60 year-olds and over in Sao Paulo. We explored the geographic characteristics using one data point per each geographic area. The descriptive analysis of the geographic characteristics was performed without the use of weights.

For the analysis of the associations between the individual, community, and health systems characteristics and polypharmacy we implemented the multi-level model described above. We implemented three different versions of each model: *Individual Models* using only individual-level covariates, *Community Models* using individual- and community-level covariates, and *Full Models* using individual, community and health systems covariates.

We ran the analytical models for each year that the survey was available (2000, 2006 and 2010). Following the sample design, we applied inverse-probability weights to all models in order to reconstruct the population of non-institutionalized individuals 60 year-old and over living in Sao Paulo in each year. In addition to individual

weights, the multilevel model also required the specification of area-level weights. Because the area-level weights had been factored in the calculation of individual weights at the time of survey design, we assumed that all areas had equal weights and we set all area-level weights equal to 1. In order to account for unequal variances we utilized robust standard errors clustered at the primary sampling units (census tracts) in all analytical models.

5.5 RESULTS

5.5.1 Sample Characteristics – Overview

The SABE sample included a total of 2,143 individuals living in 27 areas in 2000; 1,413 individuals living in 30 areas in 2006; and 1,333 individuals living in 30 areas in 2010 (Table 5.4). One of Sao Paulo sub-prefectures (Cidade Tiradentes) was not represented by participants in any of the SABE study waves. Three sub-prefectures (Ermelino Mattarazzo, Guaianases and Sao Mateus) had no participants in 2000 but had participants in 2006 and 2010. Areas without participants were not included in our analyses in the corresponding year, but were included in the years when there were participants.

Table 5.4 Overview of participants and geographic areas in the SABE study

	2000	2006	2010
Nr. of Areas	27	30	30
Nr. participants	2,143	1,413	1,133
Participants per Area			
Avg (sd)	107.7 (48.5)	63.8 (26.2)	56.8 (21.7)
Min–max	13–182	5–111	4–105

Source: SABE database.

In 2000, 107.7 participants were included on average per sub-prefecture. The sample size per area ranged from 13 to 182 in 2000. There was a tendency of decreasing sample sizes per area over time. In 2006, the average number of participants per area was 63.8 (range: 5 – 111) and in 2010 it was 63.8 (range: 4 – 105). Table 5 displays each geographic area and the corresponding sample sizes per year.

There were 4,889 observations across the three SABE survey waves. Of these observations, 2,796 (57%) individuals participated in only one survey wave; 1,408 (29%) individuals participated in two survey waves; and 685 (14%) participated in all three survey waves. We utilized information from all participants who had available data in each year, assuming that the samples were independent. We made this assumption because, 1) the majority of participants contributed information to only one survey wave; 2) because those that contributed with three waves of data were the minority; 3) because those who contributed with two waves of data were distributed across multiple years, i.e., were not concentrated in the same two waves. We provide a complete discussion of the participants and their characteristics in Chapter 4.

Table 5.5 Sub-prefectures and sample sizes in each of the survey waves

Code	Sub-Prefecture	Region	2000	2006	2010
1	Perus	North	16	9	8
2	Pirituba/Jaraguá	North	83	48	43
3	Freguesia do Ó/Brasilândia	North	78	63	44
4	Casa Verde	North	121	75	59
5	Santana/Tucuruvi	North	29	17	40
6	Jaçanã/Tremembé	North	13	15	25
7	Vila Maria/Vila Guilherme	North	177	109	79
8	Lapa	West-Central	30	25	20
9	Sé	West-Central	128	67	41
10	Butantã	West-Central	62	42	44
11	Pinheiros	West-Central	56	35	21
12	Vila Mariana	Southeast	120	77	65
13	Ipiranga	Southeast	108	63	66
14	Santo Amaro	South	92	53	35
15	Jabaquara	Southeast	53	28	40
16	Cidade Ademar	South	37	43	43
17	Campo Limpo	South	48	52	46
18	M'Boi Mirim	South	66	52	59
19	Capela do Socorro	South	74	44	43
20	Parelheiros	South	18	5	4
21	Penha	Southeast	175	111	105
22	Ermelino Matarazzo	East	.	12	10
23	São Miguel	East	68	62	73
24	Itaim Paulista	East	36	17	29
25	Mooca	Southeast	182	80	51
26	Aricanduva	Southeast	88	54	76
27	Itaquera	East	75	74	69
28	Guaianases	East	.	7	4
29	Vila Prudente	Southeast	110	56	52
30	São Mateus	East	.	18	39

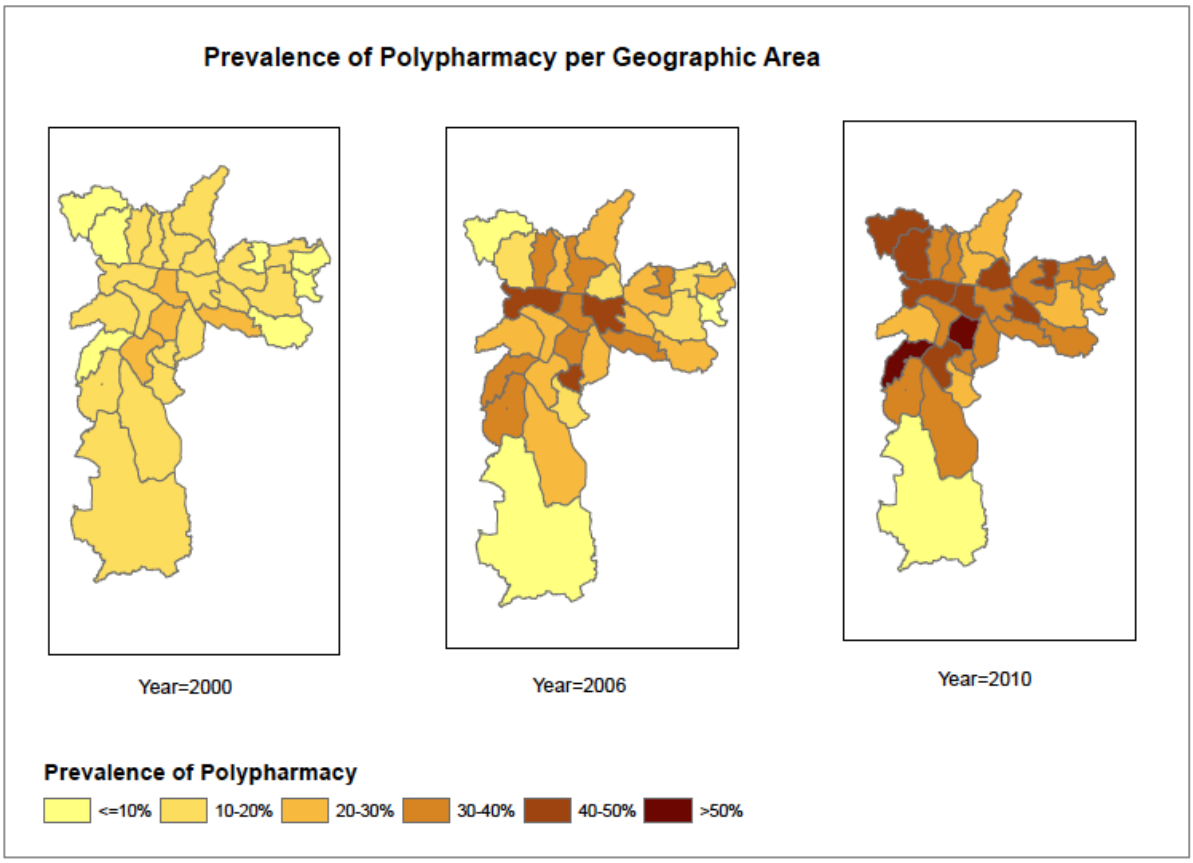
Source: SABE dataset.

5.5.2 Geographic Variation in Polypharmacy

The overall estimated prevalence of polypharmacy among individuals 60 years old and over in Sao Paulo was 16.1% in 2000 (95% CI: 14.4% - 17.9%), and 37.6% (95% CI: 34.8 – 40.4%) in 2010, a more than two-fold increase in the 10-year interval.

Across the geographic areas, the average of the area-level prevalence of polypharmacy was 15.1% (95% CI: 11.5%-18.7%) in 2000 and 36.9% (95% CI: 33.5%-40.3%) in 2010. The lowest prevalence of polypharmacy in any given area in 2000 was 1.3% and the highest was 25.1%. In 2010, the lowest prevalence of polypharmacy in a geographic area was 6.6% and the highest was 56.6% (Figure 5.3).

Figure 5.3 Prevalence of Polypharmacy among Individuals 60 years and older across the Sao Paulo Geographic Areas, 2000-2010



Source: SABE dataset. Estimated prevalence among 60 year-olds and over living in each sub-prefecture.

5.5.3 Community and Health Systems Characteristics in each Geographic Area

In the 10-year interval, the population across the Sao Paulo sub-prefectures, as reconstructed by the application of survey weights to our sample, tended to be older and sicker. The average age went from 69.6 years old to 70.8 years old. The prevalence of chronic diseases increased from 79% to 86% of the older adult population. The average number of chronic diseases per person went from 1.64 to 2.01. The average levels of symptoms and disability also increased during this period (Table 5.6).

The areas tended to be more urbanized (20% of the sub-prefectures had predominantly rural characteristics in 2000, as opposed to 11% in 2010); have higher incomes (from average of R$ 374 in 2000 to R$ 890 in 2010); and higher rates of private health insurance coverage (from 42% to 45%). Of note, both the income and the private health insurance coverage levels reflect rates among older adults only.

The availability of health resources (per 100,000 population) in an area tended to decrease in the 10-year interval, for all types of resources: physicians, health facilities and pharmacies. The population of Sao Paulo maintained a steady growth during this period, which suggests that the numbers declined because the population increased at a faster pace than the health resources.

The average number of hospitals per 100,000 people decreased from 2.84 to 2.03 in the period; the proportion of hospitals that were public changed minimally, from 35% in 2000 to 34% in 2010. The average number of hospital beds per area decreased from 466 to 322 per 100,000 people, but the proportion of hospital beds that were available to the public system increased from 41% to 45%.

The average number of public primary care clinics per area increased from 3.64 to 3.79 per 100,000 people from 2000 to 2010. In this period, there was also an increase in the number of public specialized pharmacies, from 0.64 to 0.81 per 100,000 people, but a decrease in the number of pharmacists working in the public system, from 10.4 to 9.7 per 100,000 people.

The average number of doctors per area decreased from 477 to 440 doctors per 100,000 people in the period. Generalist doctors (internists, family doctors, pediatricians, and geriatricians) decreased from 94.8 per 100,000

people to 91.2 per 100,000 people. Geriatricians were the minority of this group, and they decreased from 1.89 to 1.73 per 100,000 people. Specialists composed the majority of the workforce in all years, 80% in 2000 and79% in 2010, and their number per 100,000 people decreased from 382 to 349 in the period.

Interestingly, the indicators that reflect delivered health care (health care utilization) tended to increase over time. Average numbers of hospitalizations among older adults obtained from government sources more than doubled from 4,284 to 10,144 per 100,000 people; average rates of hospitalizations among individuals in our sample went from 6% to 11%; the rates of preventative exam increased from 40% to 73% and the rates of immunization against influenza or pneumonia increased from 61% to 80% in our sample.

Levels of enrollment in the family health program increased from 20% to 25% of 60 year-olds and over at the community level.

Table 5.6 Community and health systems characteristics of each geographic area

	2000	2006	2010	St.Diff
Predisposing Factors				
Avg. Age	69.55 (1.48)	70.17 (3.04)	70.77 (3.34)	0.33
% Women	0.59 (0.07)	0.60 (0.08)	0.60 (0.08)	0.11
% Any NCDs	0.79 (0.05)	0.86 (0.07)	0.86 (0.04)	1.12
Illness Level				
Avg. Nr. NCDs	1.64 (0.16)	1.99 (0.21)	2.01 (0.24)	1.27
Avg. Nr. Symptoms	1.49 (0.30)	1.33 (0.35)	1.57 (0.34)	0.19
Avg. Nr. Disabilities	1.26 (0.44)	1.69 (0.58)	1.62 (0.62)	0.48
Mortality 60+	3919.9 (241.3)	3574.2 (294.3)	349958 (296.4)	-1.1
Enabling Factors				
Rural Areas	0.20 (0.40)	0.10 (0.30)	0.11 (0.31)	-0.2
Avg.Per Capita Income	374.36 (211.35)	680.10 (417.64)	890.13 (588.64)	0.82
% Private H. Insurance	0.42 (0.17)	0.45 (0.17)	0.45 (0.18)	0.13
Health Resources				
Nr. Hospitals	2.84 (2.86)	2.32 (2.63)	2.03 (2.23)	-0.2
% Public Hospitals	0.35 (0.26)	0.34 (0.24)	0.34 (0.23)	-0.1
Nr. Hosp. Beds	466.2 (612.1)	379.9 (541.2)	322.4 (444.6)	-0.2
% Public Beds	0.41 (0.25)	0.46 (0.32)	0.45 (0.33)	0.09
Nr. Public 1ary Clinics	3.64 (1.15)	3.68 (0.92)	3.79 (1.04)	0.1
Nr. Public Pharmacies	–	0.64 (0.94)	0.81 (1.09)	0.12
Nr. Private Pharmacies	–	–	32.93 (17.73)	–
Nr. Pharmacists	–	10.38 (17.64)	9.71 (14.08)	-0
Nr. Doctors	–	477.6 (652.5)	440.7 (585.6)	-0
Nr. Geriatricians	–	1.89 (4.77)	1.73 (3.42)	-0
Nr. Generalists	–	94.84 (105.73)	91.21 (90.18)	-0
Nr. Specialists	–	382.71 (555.89)	349.49 (500.81)	-0
Health Care Utilization				
1ary Care Appointments	–	–	5088.8 (1563.5)	–
Specialized Care Appts	–	–	6340.1 (8336.6)	–
Hosp. admissions	4284.6 (3976.3)	15662.6 (23333.3)	10144.8 (8481.2)	0.63
% hospitalized last 12 mo	0.06 (0.03)	0.10 (0.05)	0.11 (0.06)	0.79
Avg. nr. hospitalizations	0.21 (0.10)	0.14 (0.08)	0.16 (0.11)	-0.3
% Preventative exam	0.40 (0.09)	0.56 (0.08)	0.73 (0.07)	2.79
% Immunization	0.61 (0.09)	0.74 (0.07)	0.80 (0.09)	1.45
% Births via C-section	–	0.55 (0.07)	0.58 (0.08)	0.23
% Full antenatal care	–	0.75 (0.07)	0.78 (0.06)	0.33
% Enrolled family health	–	0.20 (0.18)	0.25 (0.25)	0.14

Notes: all "count" variables are presented as number per 100,000 people (Mortality, nr. Of hospitals, beds, clinics, pharmacies, doctors, and hospital admissions.

5.5.4 Relationship between Individual and Community-Level Characteristics and Polypharmacy

In our previous work (see Chapter 4), we identified that, at the individual level, polypharmacy was strongly associated with being older, female, being in poorer health, and utilizing physician care and preventative care more often. There was no association with private health insurance, and minimal association with higher income (about 1% greater odds of polypharmacy in 2000 and 2010 associated with a R$100 difference in income).

Because these results were obtained from conditional models, they represent estimates for people living in the same geographic area (Table 5.7).

Community-level characteristics were independently associated with higher likelihood of polypharmacy. The main community-level factor associated with polypharmacy was the health insurance coverage at the area level. Higher health insurance coverage was associated with over eight times higher odds of polypharmacy in 2006 and over three times higher odds in 2010. In 2000 the association was of about 43% higher odds of polypharmacy, but it was not statistically significant. If a person had private health insurance, that fact was not significantly associated with any differences in their likelihood of polypharmacy. However, if the person lived in an area with greater health insurance coverage, then the person's odds of polypharmacy were expected to be significantly higher, and that relationship persisted after controlling for individual-level characteristics.

If two people with similar characteristics lived in areas with differed in older adult mortality rates by one death per 1,000 individuals, the person living in the area with greater deaths would be expected to have about 5% higher odds of polypharmacy in 2000, or 4% higher odds of polypharmacy in 2006, and there was no significant difference in 2010.

Table 5.7 Relationship between individual and community-level characteristics and polypharmacy

	2000		2006		2010	
	Individual	Indiv + Comm	Individual	Indiv + Comm	Individual	Indiv + Comm
Individual Characteristics						
Age	1.24**	1.23**	1.08	1.06	1.38***	1.40***
	(1.05– 1.46)	(1.03– 1.46)	(0.89– 1.31)	(0.87– 1.29)	(1.15– 1.67)	(1.15– 1.70)
Female	1.38*	1.35*	0.98	0.95	0.86	0.85
	(0.98– 1.96)	(0.95– 1.92)	(0.69– 1.40)	(0.67– 1.35)	(0.60– 1.22)	(0.60– 1.22)
Married	1.11	1.11	1.36*	1.35*	0.99	0.99
	(0.80– 1.53)	(0.82– 1.52)	(0.98– 1.88)	(0.97– 1.86)	(0.76– 1.30)	(0.76– 1.28)
Per capita Income	1.03***	1.03***	1.01	1.01	1.01*	1.01**
	(1.02– 1.04)	(1.02– 1.04)	(1.00– 1.02)	(0.99– 1.02)	(1.00– 1.02)	(1.00– 1.02)
Nr. Chronic Dis.	1.79***	1.81***	2.04***	2.05***	2.27***	2.28***
	(1.58– 2.03)	(1.60– 2.05)	(1.78– 2.35)	(1.78– 2.36)	(2.04– 2.53)	(2.04– 2.54)
Nr. Symptoms:1-2	2.31***	2.30***	1.25	1.23	1.05	1.03
	(1.58– 3.36)	(1.58– 3.36)	(0.81– 1.92)	(0.80– 1.88)	(0.76– 1.43)	(0.75– 1.41)
3+	3.12***	3.06***	1.61*	1.64*	1.55**	1.49**
	(1.83– 5.31)	(1.80– 5.22)	(0.95– 2.72)	(0.97– 2.78)	(1.09– 2.21)	(1.03– 2.14)
Nr. disabilities:1-2	1.2	1.2	1.02	1.01	0.96	0.97
	(0.83– 1.74)	(0.83– 1.72)	(0.60– 1.74)	(0.59– 1.72)	(0.73– 1.27)	(0.73– 1.30)
3+	1.35	1.36	2.46***	2.41***	1.26	1.3
	(0.87– 2.09)	(0.87– 2.10)	(1.55– 3.89)	(1.51– 3.86)	(0.81– 1.97)	(0.82– 2.07)
Priv.H.Insurance	1.31	1.31	1.14	1.13	0.86	0.83
	(0.87– 1.98)	(0.85– 2.02)	(0.82– 1.58)	(0.79– 1.60)	(0.62– 1.19)	(0.58– 1.21)
Medical visits	1.85***	1.84***	1.72***	1.68***	2.02***	2.00***
	(1.32– 2.59)	(1.31– 2.60)	(1.18– 2.51)	(1.13– 2.48)	(1.41– 2.91)	(1.38– 2.88)
Preventative Exam	1.17	1.16	1.87***	1.87***	1.13	1.14
	(0.86– 1.57)	(0.85– 1.58)	(1.33– 2.62)	(1.33– 2.63)	(0.76– 1.69)	(0.77– 1.69)
Smoking	0.67*	0.67*	0.71	0.7	0.78	0.79
	(0.44– 1.03)	(0.44– 1.00)	(0.36– 1.41)	(0.35– 1.40)	(0.47– 1.29)	(0.48– 1.32)
Alcohol	0.95	0.94	0.76*	0.76*	0.82	0.82
	(0.64– 1.40)	(0.63– 1.41)	(0.56– 1.03)	(0.55– 1.04)	(0.61– 1.09)	(0.60– 1.13)
Community Characteristics						
Mortality 60+		1.05***		1.04***		0.99
		(1.04– 1.07)		(1.03– 1.06)		(0.97– 1.01)
Rural indicator		0.84***		1.35***		0.77***
		(0.74– 0.94)		(1.20– 1.53)		(0.68– 0.89)
% Health Insurance		1.43		8.61***		3.61***
		(0.76– 2.69)		(4.87–15.25)		(2.27– 5.75)
Regression Statistics						
Constant Term	0.01***	0.00***	0.02***	0.00***	0.03***	0.04***
	(0.00– 0.02)	(0.00– 0.00)	(0.01– 0.03)	(0.00– 0.00)	(0.02– 0.07)	(0.02– 0.07)
N	2126	2126	1350	1350	1309	1309
RE Variance (se)	0.14 (0.026)	0.19 (0.027)	0.14 (0.022)	0.23 (0.031)	0.18 (0.023)	0.22 (0.035)

Notes: *p<0.10; **p<0.05; ***p<0.01 Per capita income measured in Brazilian Reais. Medical visits: indicator variable on having had more than the median number of physician health visits in the last 12 months. Preventative exam: mammogram or prostate exam in the last 24 months.

5.5.5 Relationship between Health System-Level Characteristics and Polypharmacy

While controlling for all the individual and community-level factors that we discussed above, we examined the association between polypharmacy and each of the multiple health systems characteristics. We do so by implementing adjusted models, which include for all the individual and community-level factors, plus one health system characteristic at a time. The estimates and 95% Confidence intervals of the coefficients associated with each of the variables are displayed in Table 5.8.

The magnitude and direction of the associations depended on the type of health service examined. Primary health care clinics were largely not associated with polypharmacy except for 2010, when living in an area with one additional primary care clinic per 100,000 people was associated with 7% higher of polypharmacy. The number of hospitals also was only associated with polypharmacy in 2010, when each additional hospital per 100,000 people was associated a slight decrease in odds of polypharmacy, of about 4% per cent. Because hospitals were concentrated in some areas, and there were many other areas without a hospital, we created a binary variable to identify areas with and without a hospital. When this binary indicator was used, we found significant higher odds of polypharmacy in areas with a hospital, of 135% in 2006 and about 62% in 2010. Higher number of hospital beds largely reflected the association seen between polypharmacy and hospitals, i.e., associated with slightly lower odds of polypharmacy, all other things being equal.

Living in an area that belonged to a higher quintile of private pharmacies was associated with increased odds of polypharmacy of between 26% (in 2000) to 8%; public pharmacies, however, were not significantly associated with polypharmacy.

Greater numbers of doctors per 100,000 people were associated with lower rates of polypharmacy, regardless of the doctor's specialty. An exception was Geriatricians - areas without Geriatricians were associated with 24-34% lower odds of polypharmacy in 2006 and 2010 respectively.

Living in areas where greater percentage of older adults are enrolled in a family health program was positively associated with polypharmacy in both years, but it was statistically significant only in 2006, when it was associated with 50% greater odds of polypharmacy.

Table 5.8 Health systems characteristics and their relationship with polypharmacy – adjusted for individual and community characteristics

		2000	2006	2010
FACILITIES	Nr. Public 1ary Care Clinics	0.97	1.04	1.07**
		(0.93– 1.01)	(0.97– 1.12)	(1.00– 1.15)
	Nr. Hospitals	1	0.99	0.96***
		(0.98– 1.02)	(0.95– 1.02)	(0.94– 0.98)
	Area has a hospital (y/n)	1.11	2.37***	1.62***
		(0.98– 1.27)	(1.68– 3.36)	(1.30– 2.00)
	Nr. Hospital beds	0.99	0.99*	0.98***
		(0.98– 1.00)	(0.98– 1.00)	(0.97– 0.99)
	% Public Hosp. Beds	1.21**	1.74***	1.19***
		(1.02– 1.43)	(1.44– 2.10)	(1.05– 1.34)
	Private pharmacy quintile	1.26***	1.07**	1.08**
		(1.21– 1.31)	(1.00– 1.13)	(1.01– 1.15)
	Nr. public pharmacies		0.95	1.04
			(0.88– 1.01)	(0.98– 1.10)
DOCTORS	Total Nr. Doctors		0.98***	0.96***
			(0.97– 0.99)	(0.95– 0.97)
	Nr. Generalist Doctors		0.96	0.99
			(0.92– 1.01)	(0.95– 1.03)
	Nr. Specialist Doctors		1	0.97***
			(0.99– 1.02)	(0.97– 0.98)
	Areas without Geriatrician		0.66***	0.76***
			(0.57– 0.78)	(0.70– 0.82)
FHT	% Enrolled in Family HT		1.50**	1.15
			(1.09– 2.06)	(0.93– 1.41)

Notes: Number of clinics, hospitals, hospital beds, and public pharmacies presented as per 100,000 people. Number of doctors presented as per 1,000 people. FHT: family health teams. *p<0.10; **p<0.05; ***p<0.01

Each estimate is the result of a multi-level latent variable and mixed-effects model including the variable listed, plus the following characteristics: Individual characteristics: age, gender, marital status, per capita income, private health insurance, number of chronic diseases, number of symptoms, number of activities of daily living with disability, number of physician visits in the last 12 months, preventative exam in the last 24 months, current smoking, and current alcohol use. Community characteristics: rural vs. urban indicator, average health insurance coverage among 60 year-olds and over, and mortality among 60 year-olds and over.

5.5.6 Health System-Level Characteristics and Polypharmacy: Full Models

In order to understand whether the estimates from the multiple health system factors capture similar or different underlying characteristics within the health system, we followed the conceptual model and we combined

variables related to health facilities, health workers, pharmacies, and the mix between public and private systems, in a full model (Table 5.9). All the variables that we utilized, except the number of hospitals, were not available for the year 2000. Therefore, we run the analyses on the years 2006 and 2010 only.

We selected the following variables to compose our health systems models:

- Availability of tertiary care: Indicator variable for the presence of a hospital in the area: we assume it will capture the effect of areas that have greater access to tertiary, complex care;
- Availability of physicians: Number of doctors per 100,000 people: we assume it will capture differences in the potential for delivering physician care in a given area; we believe doctors are better proxies than clinics because they may provide a better indication of volume of services;
- Provider mix: percentage of doctors who are specialists. We assume this variable will capture differences in prescribing practices that are associated with provider preferences related to their specialty;
- Private pharmacies (quintiles): we assume this variable will capture the access to pharmaceutical sales outlets, which we assume are independent from the effect of physicians and hospitals in an area;
- Presence of the public health system: percentage of seniors enrolled in a family health program in an area: we assume that this variable will capture difference in the mix of services in an area between the public and the private health systems; the distribution between the two systems correlates with area-level socio-economic status and the levels of care predominantly offered in a geographic area, as follows: lower socio-economic status -> greater availability of public care relative to private care-> greater availability of primary care as opposed to tertiary care -> higher rates of enrollment in the family health program.

Table 5.9 displays the findings from our full models, as well as the findings from the individual models and individual + community models, for comparison.

When controlling for all individual and community characteristics, the presence of hospitals, presence of private pharmacies, and level of enrollment in the family health program were positively and statistically significantly associated with higher odds of polypharmacy. Higher number of doctors per 100,000 people was negatively and

statistically significantly associated with the odds of polypharmacy. Because these are conditional models, the estimates reflect the expected associations for an area with the average outcome (polypharmacy).

A person with the same individual characteristics, living in an area with the same rural/urban profile, same levels of mortality and same levels of insurance coverage as another person, would be expected to have about two times higher odds of polypharmacy if he/she lived in an area that had a hospital (in 2006) or about 30% higher odds in 2010 (not statistically significant). If the areas differed by one quintile of the distribution of private pharmacies, the individual living in the area with higher quintile would be expected to have about 36% higher odds of polypharmacy (in 2006) or 15% (in 2010).

If the areas differed in number of providers, the individual living in the area with one more provider per 100,000 people would be expected to have 3% lower odds of polypharmacy (in 2006) and 2% lower odds of polypharmacy in 2010. Whether these physicians were composed of a greater number of specialists did not seem to be associated with any statistically significant differences in the odds of polypharmacy.

Lastly, if one of these individuals lived in an area with greater coverage of the family health program, they would be expected to have twice the odds of polypharmacy in 2006 and about 50% higher odds of polypharmacy in 2010. It is important to mention that a 1-unit change in a variable that is a proportion indicates the expected odds ratios comparing an area with 100% and another area with 0% of the variable. In this case, if all seniors in one area enrolled in the FHT versus if no seniors had enrolled in the FHT.

The magnitude, sign, and statistical significance of between each of the health system variables and polypharmacy were not greatly modified by the presence of the other health system variables in the model; the variable that changed the most was the presence of hospitals, which decreased in magnitude, and lost the statistical significance in 2010. Especially the number of doctors maintained very stable estimates unaffected by the other variables that were added to the model.

The individual-level factors estimated in our individual models did not exhibit significant modifications after the introduction of the community characteristics or after the introduction of the health systems characteristics. The magnitude, sign and statistical significance, were mostly unchanged across the three model specifications.

The community-level characteristics, however, had their associations with polypharmacy modified after the introduction of the health systems variables in the models. The most remarkable case was the indicator variable for rural/urban profile of a geographic area. This coefficient changed magnitude, direction, and lost the statistical significance once the health system variables were entered into the model. It is possible that the health systems characteristics at the area level may be the real drivers of the differences in the odds of polypharmacy, which are captured by a rural/urban indicator in the absence of more specific information in the models.

The large coefficients associated with higher private insurance coverage at the area level also had their magnitude reduced when the health systems variables were accounted for. The coefficient for private insurance coverage in 2006 was reduced by 32%, and the coefficient for private insurance coverage in 2010 was reduced by 11% in the full model, raising the possibility that at least some of the effect captured by the health insurance coefficient may be due to differences in the characteristics of the health services available at the area level – such as accessibility and availability.

Remarkably, however, much of the effect of private health insurance coverage was maintained even after the inclusion of the full set of health systems characteristics, suggesting that there may be other sources of difference in the propensity for polypharmacy associated with higher rates of private insurance at the area level that we have not accounted for in our models.

The estimates for mortality rates were also modified when the health systems variables were added to the models. The estimates in both years became more negative – the coefficient in 2006, which was positive, went towards the null hypothesis, and the coefficient in 2010, which was negative, became even more negative, and acquired statistical significance. Our models are not equipped to address possible mechanisms that could explain why these changes have occurred. Elucidating the possible role of community illness levels in the occurrence of polypharmacy in particular, and health services utilization in general, should be the focus of future studies.

Table 5.9 Full models including multiple supply-side health systems factors and their comparison to individual models, and individual + community models

	2006			2010		
	Individual	**Indiv + Comm**	**Ind+Com+Hsys**	**Individual**	**Indiv + Comm**	**Ind+Com+Hsys**
Individual Characteristics						
Age	1.08	1.06	1.05	1.38***	1.40***	1.38***
	(0.89– 1.31)	(0.87– 1.29)	(0.85– 1.28)	(1.15– 1.67)	(1.15– 1.70)	(1.14– 1.67)
Female	0.98	0.95	0.99	0.86	0.85	0.87
	(0.69– 1.40)	(0.67– 1.35)	(0.69– 1.42)	(0.60– 1.22)	(0.60– 1.22)	(0.61– 1.23)
Married	1.36*	1.35*	1.35*	0.99	0.99	0.97
	(0.98– 1.88)	(0.97– 1.86)	(0.97– 1.88)	(0.76– 1.30)	(0.76– 1.28)	(0.74– 1.26)
Per capita Income	1.01	1.01	1.01	1.01*	1.01**	1.01*
	(1.00– 1.02)	(0.99– 1.02)	(0.99– 1.02)	(1.00– 1.02)	(1.00– 1.02)	(1.00– 1.01)
Nr. Chronic Dis.	2.04***	2.05***	2.05***	2.27***	2.28***	2.26***
	(1.78– 2.35)	(1.78– 2.36)	(1.78– 2.35)	(2.04– 2.53)	(2.04– 2.54)	(2.03– 2.52)
Nr. Symptoms:1-2	1.25	1.23	1.19	1.05	1.03	1.02
	(0.81– 1.92)	(0.80– 1.88)	(0.77– 1.84)	(0.76– 1.43)	(0.75– 1.41)	(0.74– 1.41)
3+	1.61*	1.64*	1.59*	1.55**	1.49**	1.50**
	(0.95– 2.72)	(0.97– 2.78)	(0.94– 2.69)	(1.09– 2.21)	(1.03– 2.14)	(1.03– 2.18)
Nr. disabilities:1-2	1.02	1.01	1.03	0.96	0.97	0.97
	(0.60– 1.74)	(0.59– 1.72)	(0.60– 1.76)	(0.73– 1.27)	(0.73– 1.30)	(0.73– 1.31)
3+	2.46***	2.41***	2.30***	1.26	1.3	1.27
	(1.55– 3.89)	(1.51– 3.86)	(1.44– 3.70)	(0.81– 1.97)	(0.82– 2.07)	(0.80– 2.02)
Priv.H.Insurance	1.14	1.13	1.11	0.86	0.83	0.83
	(0.82– 1.58)	(0.79– 1.60)	(0.78– 1.58)	(0.62– 1.19)	(0.58– 1.21)	(0.57– 1.20)
Medical visits	1.72***	1.68***	1.66**	2.02***	2.00***	2.01***
	(1.18– 2.51)	(1.13– 2.48)	(1.13– 2.44)	(1.41– 2.91)	(1.38– 2.88)	(1.40– 2.90)
Preventative Exam	1.87***	1.87***	1.92***	1.13	1.14	1.14
	(1.33– 2.62)	(1.33– 2.63)	(1.35– 2.73)	(0.76– 1.69)	(0.77– 1.69)	(0.77– 1.70)
Smoking	0.71	0.7	0.72	0.78	0.79	0.81
	(0.36– 1.41)	(0.35– 1.40)	(0.36– 1.44)	(0.47– 1.29)	(0.48– 1.32)	(0.49– 1.36)
Alcohol	0.76*	0.76*	0.76*	0.82	0.82	0.82
	(0.56– 1.03)	(0.55– 1.04)	(0.55– 1.05)	(0.61– 1.09)	(0.60– 1.13)	(0.60– 1.12)
Community Characteristics						
Mortality 60+		1.04***	1.01		0.99	0.98***
		(1.03– 1.06)	(0.99– 1.03)		(0.97– 1.01)	(0.96– 0.99)
Rural indicator		1.35***	1.07		0.77***	1.07
		(1.20– 1.53)	(0.90– 1.26)		(0.68– 0.89)	(0.91– 1.25)
% Health Insurance		8.61***	5.90***		3.61***	3.18***
		(4.87–15.25)	(3.57– 9.75)		(2.27– 5.75)	(1.95– 5.19)
Health Systems Characteristics						
Hospital Indicator			1.96**			1.32
			(1.09– 3.52)			(0.76– 2.29)
Private Pharmacy Quintiles			1.36***			1.15***
			(1.24– 1.48)			(1.09– 1.20)
Nr. Doctors/1,000 pop.			0.97***			0.98***
			(0.96– 0.98)			(0.98– 0.99)
% Specialists			1.03			0.98
			(0.94– 1.13)			(0.89– 1.08)
% Enrolled in FHT			1.97***			1.48***
			(1.56– 2.48)			(1.24– 1.76)
Regression Statistics						
Constant Term	0.02***	0.002***	0.002***	0.03***	0.04***	0.033***
N	1350	1350	1350	1309	1309	1309
RE Variance (se)	0.14 (0.022)	0.23 (0.031)	0.18 (0.028)	0.18 (0.023)	0.22 (0.035)	0.10 (0.027)

Notes: Number of clinics, hospitals, hospital beds, and public pharmacies presented as per 100,000 people.

Number of doctors presented as per 1,000 people.

*p<0.10; **p<0.05; ***p<0.01

Each estimate is the result of a multi-level latent variable and mixed-effects model including the variable listed, plus the following characteristics: Individual characteristics: age, gender, marital status, per capita income, private health insurance, number of chronic diseases, number of symptoms, number of activities of daily living with disability, number of physician visits in the last 12 months, preventative exam in the last 24 months,

current smoking, and current alcohol use. Community characteristics: rural vs. urban indicator, average health insurance coverage among 60 year-olds and over, and mortality among 60 year-olds and over.

These findings suggest that more complex care – as the care delivered in hospitals – may be associated with polypharmacy. Greater availability of commercial establishments, where individuals can purchase drugs out-of-pocket and without a medical prescription - such as in areas with higher concentration of private pharmacies – may also be associated with polypharmacy. And greater accessibility of care, such as the one represented by the greater enrollment in the family health program, may also be associated with polypharmacy. Taken in isolation, these findings suggest that polypharmacy behaves like a supply-sensitive form of care. Supply-sensitive care tends to increase in utilization as the availability of resources increases in a given local area.

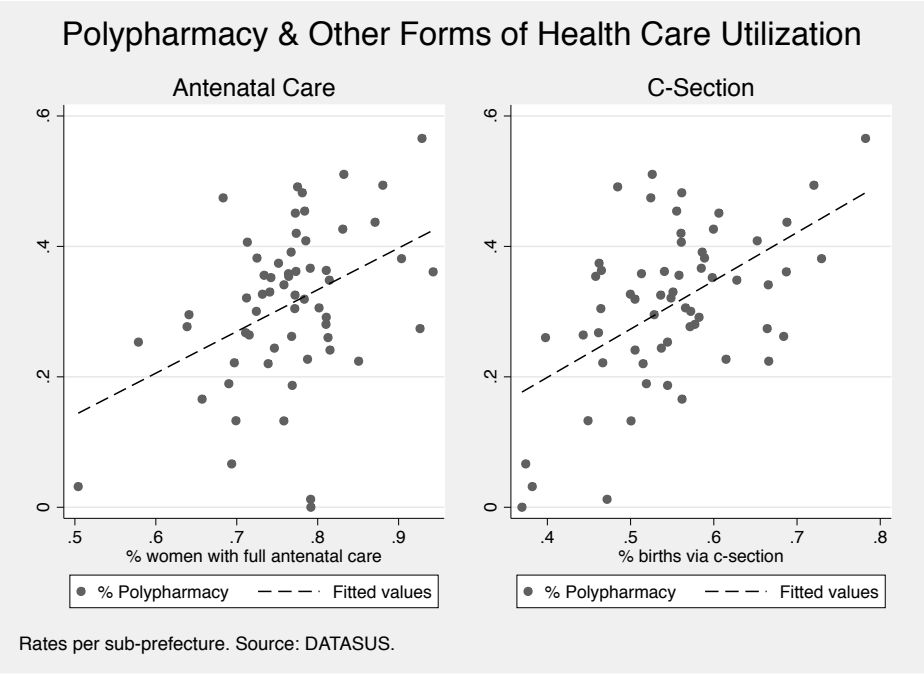
In contrast to these findings, however, polypharmacy was negatively associated with availability of doctors: areas with more doctors tended to have lower polypharmacy, all other things being equal. The interpretation of this, as well as all other findings, depends on the assumptions that we make about the data. If more doctors truly reflect greater availability of physician care for the population, it is possible that greater number of doctors can provide better opportunities for monitoring of pharmaceutical treatments, and more opportunities to manage and reduce drug utilization.

On the other hand, higher number of doctors may not reflect greater availability of physician care for the population. The information on number of doctors was available only for the professionals who worked in the public sector. If areas that have more doctors in the public sector also had less doctors in the private sector, and if there were too many barriers to entry for patients seeking care in the public sector, the higher number of doctors would effectively be a marker of less physician care to the population. We find this hypothesis unlikely, as we investigated another marker of the care delivered by the public health system (proportion of seniors enrolled in FHTs), and it was associated with higher odds of polypharmacy.

5.5.7 Polypharmacy: A Form of Supply-Sensitive Care?

Provider prescription practices are a significant component of the drivers of geographic variation in health care utilization and could not be adequately addressed in our analysis. In order to elucidate the possible mechanisms being captured by our findings we perform an additional descriptive analysis. We compare polypharmacy to a form of effective care: percentage of pregnancies with full antenatal care, and we compare polypharmacy to a form of supply-sensitive care typical of the Brazilian context: the very high rates of C-sections (Figure 5.4). Each data point represents one geographic area (sub-prefecture). Both years for which data was available - 2006 (proxy: 2007) and 2010 - are included in the figure.

Figure 5.4 Polypharmacy vs. antenatal care (effective care), and C-sections (supply-sensitive or preference-sensitive care)



Polypharmacy had a positive and moderate correlation with both forms of health care utilization: the correlation between polypharmacy and C-sections was 0.44, and the correlation between polypharmacy and full antenatal care was 0.36. However, polypharmacy did not exhibit a clear correspondence with either of these forms of care. An important caveat is that the providers who make decisions on obstetrics are not the same as those who make decisions regarding the care of older adults. However, these providers may interact in similar care networks and be influenced by each other's behaviors and prescribing preferences.

The strong association between polypharmacy and the various measures of health care availability indicate that it may be a form of supply-sensitive care. Our study did not directly address provider preferences, which may be a significant driver underlying some of the results that we found, and should be the focus of future studies.

5.5.8 Explaining Variation in Rates of Polypharmacy

In order to quantify the variance accounted for by each of the set of predictors we implemented a sequence of estimations using the total number of drugs that the SABE participants were taking. While the number of medicines and the likelihood of polypharmacy are closely related, these are not the same metric.

We first implemented null models (no predictors) of the count of drugs that a person was taking, adding only a random intercept for sub-prefecture. Next, we implemented a similar model with all the individual-level covariates (see Table 5.9). Finally, we implemented the same model adding all individual predictors as well as all community- and health systems- covariates. We implemented this analysis for 2006 and 2010 only, as these two years were the only ones with full information on all the health system covariates.

We find that, in 2006, individual characteristics explained 23% of the variance in polypharmacy. The addition of the full set of community and health systems variables to the model explained an additional 0.6% of the variance in polypharmacy. In 2010, individual characteristics explained 26% of the variance in polypharmacy. The addition of the full set of community and health systems variables to the model explained an additional 0.2% of the variance in polypharmacy.

It is important to mention that the proportion explained by the health system and community characteristics is not a percentage of the total variation in polypharmacy; rather, it is the proportion of the variance remaining after the variance explained by the individual factors had already been accounted for.

5.6 DISCUSSION

Our study contributed to the understanding of the health systems characteristics associated with polypharmacy among Sao Paulo older adults. Polypharmacy was associated with presence of hospitals, higher concentration of private pharmacies, and higher enrollment in family health programs in a given geographic area. Polypharmacy was inversely associated with the number of physicians in a geographic area, but was not associated with physician specialty mix. We also demonstrated that some health systems characteristics may underlie the associations between living in rural areas and differences in health care utilization that are a frequent finding of health care utilization studies.

We found that a significant proportion of the variation in overall drug utilization (total number of drugs per person) was accounted for by individual -level characteristics. Individual characteristics explained 23% of the variation in 2006; community and health systems characteristics explained an additional 0.2% of the remaining variance. In 2010, the numbers were very similar: 26% of the variation in drug utilization was explained by individual -level characteristics; community and health systems characteristics explained an additional 0.6% of the remaining variance.

These numbers do not mean that the set of health systems and community characteristics are not relevant in the Sao Paulo context; their main message is that, proportional to individual characteristics, the specific indicators that we studied were not associated with enough variation in the outcome in order to explain more cases. One of the reasons why this could be the case is if we did not capture the correct variables.

Another possibility is that there may be measurement error in the variables, such as the private pharmacy quintiles, that are a proxy, but do not reflect the actual levels of the factors at the time of the survey. Is it possible that the main contribution from the health systems variables is not their effect sizes; rather, it's the qualitative finding of which characteristics are linked with polypharmacy, which matters as an indication of pathways that should be pursued in the future.

Another possibility is that the low percentage of variance explained by area-level characteristics may be a product of the low sample sizes per area. The SABE study was not meant to capture geographic variation outcomes. Therefore, the sample sizes at the geographic-area level were some times very small, not having enough power to allow correlations to emerge. New studies using other data sources such as electronic health records from the Sao Paulo Health Secretariat and others may be better equipped to address these questions.

Even with these limitations, our study provided a contribution to the Andersen model: by identifying the associations between health system's factors and polypharmacy while controlling for individual factors, we demonstrated that there might be direct pathways through which health system factors may influence the occurrence of polypharmacy independently from an individual's actions or characteristics. The possibility of direct pathways should be incorporated in the model and examined by future studies.

5.7 LIMITATIONS

Although some health systems characteristics are correlated with polypharmacy, there is still a large proportion of the variation that remains unexplained. It is possible that polypharmacy may be a supply-sensitive form of health care utilization in this context. Supply-sensitive forms of health care utilization are driven in large part by preferences and practices of health providers, which we were not able to address in our analyses.

We were also not able to address other health system factors that may be key to understand the occurrence of polypharmacy in the Sao Paulo context. Within the Andersen health behavior model, for example, there were factors that we were not able to address:

Societal Factors – such as technology and norms, could influence polypharmacy. We assumed that these factors were fixed; we assumed there would be little variation across areas of the same city. However, technology and norms could vary over time. Drugs enter the market, industry invests in marketing, government formularies expand, cultural acceptability increases, prices fluctuate, generics and other forms become available; government programs are established, etc. All these factors could have greatly changed in 10 years. It would be

important to address these factors, as changes in technology and norms are more likely to impact changes in the use of polypharmacy than changes in the underlying health conditions of the population over time. Even if chronic diseases are increasing in prevalence, higher availability of treatments may modify patients and doctors preferences and perceptions, may make the drugs more desirable and acceptable, and may influence their use. Future studies such as interrupted time series and differences-in-differences could be implemented to analyze polypharmacy pre- and post- certain strategic policies. However, with 3 years this is not possible in our study.

Distribution of services – our multilevel analysis implicitly incorporated the assessment of health systems resources distribution across areas. However, we did not know the distribution within a given geographic area. This is a limitation of our study that could be addressed by future geographic analyses studies using geo-location information on the multiple health services.

Volume of resources – the level of doctors and health facilities relative to the size of the population in each area influences polypharmacy. We chose to use the general population (as opposed to only the population of older adults) because we reasoned that health resources have to attend to the demand of multiple sources in that setting, that spend the entire population. Even for geriatricians, who in theory would serve only older adults, having the general population as a denominator is relatable to policy makers and standardized, so it can be a more meaningful metric. However, we did not have the full set of facilities and providers from the private sector. This was a significant limitation of our work, as about half of the Sao Paulo population is privately insured. Differences in private services may be captured by the area-level health insurance effects in our analysis, which were very large in magnitude and remained statistically significant throughout the models.

Structure – the structure component reflects "what happens to the patients after they enter the system". An important component of the structure of the health system is the level of integration and coordination across services. This is especially important in the case of polypharmacy, where close and integrated monitoring of treatments is important in order to avoid drug risk. We could not address this characteristic. Studies that examine provider networks would be more equipped to address this characteristic.

Access – We believe that it is of paramount importance to understand the differences in polypharmacy across the public and private health systems in Brazil. These two systems have a different set of barriers to entry that

represent significant access differences. For example, in the public health system, access is limited by barriers associated with health care responsiveness; there are long queues, and multiple administrative hurdles. In the private health system, access is mostly limited by ability to pay. In our study, we tried to fit everything in one model, which may have been a limitation. There may not be one single model that explains polypharmacy for the entire population. Subgroup analyses in future studies could focus on investigating how the multiple determinants affect the population of exclusive users of the public and the private systems.

Provider behavior – provider's preferences and prescribing practices could also vary across the public and private systems. In the public system however the providers are salaried; they do not have the same need to prescribe in order to maintain clientele. However, they may be overworked and may not provide adequate monitoring of polypharmacy regimens. In the private system providers are not restricted to a formulary, they are targeted by the pharmaceutical industry and can provide samples, for example. But they may be more limited by drug prices, and they may want to satisfy their client so that they don't lose business. It would be important to assess whether there are significant differences in provider prescribing behavior across the public and the private health system that could affect polypharmacy. Qualitative studies such as in-depth interviews with providers might help clarify these questions.

In addition, we did not address all dimensions of access. Others have proposed that access is a combination of multiple disaggregated dimensions: availability, accessibility, accommodation, affordability, and acceptability of services . In the case of polypharmacy these relevant aspects of access to care would be represented by:

- Availability: number and type of pharmaceutical products in the private market; drug formularies and drug shortages in the public system.
- Accessibility: proximity of providers and pharmacies to a person's place of residence;
- Accommodation: barriers to accessing drugs and medical services – those would mostly apply to individuals who depend on the public health system to obtain medicines. For example, long queues, paperwork, short opening times, etc. In the private health system, the main barriers to access drugs are requirements put forth by the pharmaceutical regulatory agency, for example special protocols that have to be followed in order to purchase certain controlled substances.
- Affordability: drug prices (very important because most drug expenditures are out-of-pocket in Brazil).

- Acceptability: cultural practices and beliefs, both from patients and providers, related to drug utilization.

Because we did not have such information, we were not able to include it in this study. However, it is important to assess both supply and demand factors, as both of these factors interfere with the likelihood of polypharmacy (Peters, 2008); also, these are likely to be correlated. Patients with higher propensity to polypharmacy might self-select into obtaining care from providers with greater propensity to prescribe polypharmacy. More availability of pharmacies could increase acceptability and desirability of drugs, creating supply-induced demand.

These factors would be a very relevant analysis and it should be pursued by future studies. For example, qualitative methodologies could address all these components in great detail. Qualitative studies could help understand how those factors interact with each other and how they affect polypharmacy. This could complement our study and would be especially important because of the high level of decentralization of the public health care system in Brazil – making the inferences from secondary data such as ours very limited.

Lastly, we did not assess equity in health care utilization (equity in access). But, our results indicated that income at the individual level was not associated with polypharmacy. This was in opposition to several other studies, especially in Brazil (Coelho Filho et al., 2004), which have shown that polypharmacy is associated with greater socio-economic status. One of the factors that may underlie this finding is that the public health system may be succeeding in making pharmaceuticals more accessible to the individuals who cannot afford them. The question is whether the public system provides the necessary monitoring for these treatments.

5.8 POLICY IMPLICATIONS AND FINAL CONSIDERATIONS

Our findings support the possibility that at least some of the utilization of polypharmacy may exhibit a pattern of supply-sensitive care. Individual characteristics, including health need, accounted for about a quarter of the variation in drug use that we measured across the Sao Paulo sub-prefectures. Polypharmacy was associated to many health system's characteristics that are linked to availability and complexity of care. However, they explained only a small portion of the variance.

It is likely that the ultimate occurrence of polypharmacy is a combination of patient preferences, provider practices, health need, and the constraints and limitations of the health system where they interact. From a public health perspective, understanding that not all polypharmacy is driven by need is important in order to devise strategies to improve monitoring and provide opportunities for review and discontinuation of treatments.

Historically, Brazilian policy-makers have focused on expanding access to medicines. The current trends in polypharmacy, especially among older adults, indicate that it is time to focus on improving appropriateness of treatments – the prescription of the right drug, for the right indication, in the right dosage, and for the right duration – and improving opportunities for treatment monitoring. The ultimate goal is to balance the benefits and the risks of pharmaceutical treatments.

The present study contributed to informing future policies in Sao Paulo by, first, demonstrating that health systems factors can be associated with polypharmacy independently on individual characteristics; this opens the possibility that modifications at the health systems level may influence polypharmacy at a population level. Second, we demonstrated that the greater availability of doctors in the public health system in Brazil is correlated with lower odds of polypharmacy. This finding holds for the public health system even after controlling for individual characteristics, and might provide a policy target to be explored. Perhaps better training of health professionals, better practice guidelines, or simply greater availability of physician care for the older adult population may provide opportunities to curb polypharmacy and its risks. Third, the strong association between polypharmacy and the density of private pharmacies per area indicates that private pharmacies may also be a potential policy target where policies to reduce polypharmacy could focus on. Improving regulations and seizing the pharmaceutical encounter as an opportunity to inform patients, review treatments and reduce risk would be a low-cost solution that may attend to patient preferences. Lastly, the association that we identified between polypharmacy and higher enrollment in the family health program, a mainstay of the public health system in Brazil, indicates that policy-makers should develop a thorough assessment of the program and make sure that it meets the needs of its beneficiaries without increasing health risk.

6. CHAPTER VI: DISCUSSION

6.1 SUMMARY OF FINDINGS

Our study contributed to the understanding of trends and determinants of polypharmacy among older adults in Sao Paulo, Brazil, as well as the association between polypharmacy and drug risk in this population.

Our main findings were:

1. Drug utilization among older adults in Sao Paulo was very frequent, and grew significantly between 2000 and 2010

- Use of one or more drugs per day increased from 84% to 91%
- The average number of drugs increased from 2.5 to 3.9 drugs/day per person
- The prevalence of polypharmacy (five or more drugs per day) went from 16% to 38%, a more than two-fold increase
- The prevalence of taking ten or more drugs a day went from 0.7% to 4.5%, an almost 8-fold increase
- The prevalence of polypharmacy with at least one drug risk criterion went from 13% to 23%, almost doubled

2. Drug risk was very frequent and was a special concern among persons with polypharmacy

- The risks examined were: drug-drug interactions, anticholinergic adverse effects, and potentially inappropriate prescribing
- About two-thirds of people with polypharmacy were exposed to some form of drug risk, and the risk increased with higher numbers of drugs in use
- The number of persons with polypharmacy with at least one risk criterion decreased over time, from 77% to 60%
- The Beers Criteria identified most of the risk, but it was an incomplete metric; other risk metrics contributed to the identification of drug adverse effect potential.

- While the risk identified by the Beers Criteria reduced over time, the risk identified by other metrics increased
- There was not a specific drug or combination underlying most of the risk associated with polypharmacy

3. Polypharmacy was associated with having greater number of chronic diseases, being in worse health, using greater levels of health services, being older, and being female

- Rates of polypharmacy grew faster among men
- Women had lower odds of polypharmacy associated with each additional chronic disease than men
- Inappropriate polypharmacy had same determinants

4. There was significant geographic variation in polypharmacy across the 30 Sao Paulo sub-prefectures.

- Individual characteristics helped explain the most, about 25% of geographic variation, of total number of drugs per day
- Community characteristics and health systems factors together explained an additional 0.2%-0.6% of the variance
- There's still significant variation unexplained
- Main community factors associated with polypharmacy were: rural area, higher income, higher health insurance coverage, and higher senior mortality
- Community factors were directly associated with polypharmacy, remained when controlling for individual factors
- Having private health insurance did not change the likelihood of polypharmacy, but living in an area with higher health insurance coverage greatly increased the likelihood of polypharmacy

5. Presence of hospitals, higher number of private pharmacies, and higher enrollment in the family health program were associated with greater polypharmacy. Higher number of doctors in the public system was associated with lower polypharmacy.

- Health systems characteristics were associated with polypharmacy even when controlling for individual factors

- However, these characteristics do not explain a significant portion of the variation in the utilization of polypharmacy
- Higher health insurance coverage at the area level probably indicated greater availability of private services or differences in providers' practices
- Polypharmacy is likely a combination of patient preferences, provider practices, health need, and the constraints and limitations of the health system where they interact
- From a public health perspective, understanding that not all polypharmacy is driven by need is important in order to devise strategies to improve monitoring and provide opportunities for review and discontinuation of treatments

6.2 INTERPRETATION

Our study was innovative in that we utilized a multi-level model in order to simultaneously explore the relationships between polypharmacy and both individual and area-level characteristics, including at the health system's level. We demonstrated that, first, polypharmacy among older adults should be a public health concern in Sao Paulo. Policies to reduce drug risk should target all older adults with polypharmacy.

Even though individual-level factors explained the largest part of variation in drug use, area-level and health systems characteristics influenced polypharmacy independently from individual factors.

This finding presents an important contribution to the literature. Many studies investigate individual characteristics only. Individual factors do not fully explain the occurrence of polypharmacy. Future studies aiming to elucidate the determinants of polypharmacy in other contexts should make sure to examine area-level as well as individual-level characteristics.

Area-level characteristics should also be part of the conceptual framework of polypharmacy utilization, and both area-and health systems characteristics should be allowed to have direct associations with the outcome of health care utilization (in this case, polypharmacy), as they do remain after adjusting for individual-level factors.

Although our study was able to demonstrate the independent effect of area-level characteristics on the occurrence of polypharmacy, we were not able to elucidate the mechanisms through which these associations occur. Future studies should focus on clarifying these mechanisms, so that better policies can be implemented to protect older adults from drug risks associated with polypharmacy in Sao Paulo.

Pathways through which health systems characteristics could influence polypharmacy 'directly', i.e., without being mediated by individual factors, would be, for example, through provider preferences. If two individuals access the same number of physician visits but one physician is more aggressive in their prescribing practices, than that will influence polypharmacy differently, for the same level of patient utilization. Qualitative investigations, especially those exploring patient preferences and physicians' prescribing practices, may provide a significant contribution to reveal possible mechanisms through which these associations occur.

We identified a decrease in the levels of drug risk associated with polypharmacy over time. This is a new finding that added to the existing knowledge about polypharmacy trends in Brazil. We believe that the decrease in the levels of drug risk associated with polypharmacy is likely to reflect changes in drug selection over time. The characteristics and determinants of this finding in the Sao Paulo context are yet to be fully understood and should be explored in future investigations. A similar finding had been previously described among older adults in France and was attributed to policies implemented to improve prescribing among older adults (Bongue, 2009).

Our study contributed to future investigations by demonstrating that it is important to employ multi-dimensional measurements of drug risk when investigating persons with polypharmacy. Temporal trends in the association between polypharmacy and drug risk varied markedly according to the drug risk metrics that we utilized. Uni-dimensional measurements may paint an incomplete picture of the potential risks of polypharmacy and should be avoided.

6.3 LIMITATIONS

This study has several limitations. First, the cross-sectional nature of our study did not allow us to establish causation between the multiple factors that we examined and the occurrence of polypharmacy. Still, we call our findings "determinants" of polypharmacy because there is theoretical basis to explain the possible causal pathways between each of the factors and polypharmacy; the conceptual framework postulates these as causal relationships; and there is empirical evidence from previous studies supporting causal relationships between these characteristics and polypharmacy.

Still, we cannot rule out the possibility of bi-directionality or reverse causation in the associations that we identified. For example, even though the literature consistently describes worse health as leading to polypharmacy, we cannot rule out the possibility that polypharmacy might lead to poor health. Our study empirically demonstrated that polypharmacy is associated with increased risk of adverse effects and drug interactions. While persons with poor health may be prescribed more drugs to alleviate their conditions, it is also possible that persons taking more drugs might feel clinically worse-off because of adverse effects and might report being in worse health.

Or, individuals who seek greater number of physician visits may be prescribed more drugs, resulting in polypharmacy. Individuals with polypharmacy might develop adverse effects, requiring more physician visits, which in turn may result in the prescription of more drugs.

Such feedback loops have actually been demonstrated to be true in some cases, and their result – a prescribing cascade – is considered a serious potential complication from polypharmacy. The occurrence of prescribing cascade among older adults with polypharmacy in Sao Paulo should be quantified in future studies. Longitudinal studies would be the best way to address this phenomenon, as they allow for the sequence of events to be recorded over time.

At the area level there is also potential for the associations that we found to be a product of reverse causation. This would be the case if individuals with greater propensity for polypharmacy would choose to live closer to

hospitals and services, for example. This possibility seems unlikely, but it could be explored in future studies. An analytical approach that might help elucidate these relationships would be the use of instrumental variables.

Also, there might be unmeasured characteristics that could have distorted our results if they affected both the occurrence of the factors that we examined and the likelihood of polypharmacy (residual confounding). For example, if prices of pharmaceuticals varied according to the availability of health services in an area. If drug prices were higher in rural areas, and rural areas tended to have low levels of health services, we might be incorrectly attributing the low rates of polypharmacy to lower availability of services, when in fact higher drug prices in those areas were the main explanation.

We believe that the possibility of residual confounding is unlikely, however. We controlled for a wide range of individual- and area-level characteristics in our models; and all the areas that we examined were part of the same city. It would be unlikely to have substantial variations in price across areas of the city given that the sales tax is the same across all areas, most private pharmacies are part of commercial chains that have multiple units across different areas, and because people might respond to higher drug prices by purchasing medicines in more central areas of town, in the areas where they work, for example.

Second, the source of our data was a household survey originally implemented to investigate other aspects of health and wellbeing, not drug utilization. However, the survey collected comprehensive information on drug use, both via self-report and via direct observation of medicine cabinets and pill boxes. Drugs were recorded using a standardized international classification that greatly contributed to data quality. All survey participants contributed information on drug use; there were no missing values regarding drug utilization. The survey also collected a very comprehensive set of individual characteristics including multiple indicators of socio-economic, health, behavioral and health utilization characteristics.

The survey mostly relied on self-reported information. Yet, self-reported use of medications is considered reliable, especially when the information was objectively cross-checked by the researchers (Landry et al., 1988). Self-reported survey data has been successfully employed in investigations of various aspects of elderly health, including drug utilization and clinical conditions. Because medical prescriptions are not always required in

Brazil, and are often not followed, the method of self-report was likely to reflect actual drug utilization, which was the object of our study.

Only prescription and over the counter drugs were included in our analyses. Although the survey collected extensive information on other pharmaceutical products, general labels were used to specify only the category of other pharmaceutical products. Hence, we could not identify active ingredients of herbal, homeopathic, and compounded products, and we were not able to include them in our analysis.

Empirically, the use of other pharmaceutical products was much less frequent than prescription and over-the-counter drugs in our sample. The use of herbal, homeopathic, and compounded products was not different across persons with and without polypharmacy, and tended to decrease over time in both groups. Also, focusing on prescription and over-the-counter drugs was in line with most of the literature with polypharmacy, facilitating the comparability of our results.

Our study did not have information on drug dosage and posology, preventing us from addressing issues such as drug toxicity and medication errors. However, most studies with polypharmacy have demonstrated that the higher number of drugs in a pharmaceutical regimen is a problem of its own, mostly related to drug selection and monitoring. The literature also indicates that drug toxicity is not a frequent source of drug burden (Edwards & Aronson, 2000). There was also no information regarding the duration of the treatments – whether the individuals were taking the reported drugs for a couple of days or for longer periods of time. Given the very high number of drugs reported – up to 17 – and the types of drug classes involved – mostly cardiovascular, neuropsychiatric, and metabolic drugs - we find it likely that these were long-term regimens.

Third, the survey was not designed to test for geographic variation. The sample size was calculated to represent the population of the entire city of Sao Paulo in each year. The study was not powered to look at differences across areas. Indeed there were areas with as little as five participants in our sample. This fact could probably have skewed our results towards the null hypothesis (type 1 error). Because sub-prefectures play an important role in the management of the public health system, future studies should consider stratifying their sampling processes by sub-prefecture, to ensure representativeness at the sub-prefecture level.

Each year, there were only 30 geographic areas contributing level-2 information to our analyses (sub-prefectures). Some characteristics, such as the prevalence of health insurance and the presence of private health services, may be correlated at the area level; therefore, there might not have been enough covariance patterns across the areas, and some analyses may have relied on extrapolation. This could have biased our results. Some approaches to mitigate this possibility, such as propensity scores and matching methods, might be explored in futures studies.

Fourth, our choice of sub-prefectures as the level -2 unit of analysis was motivated by the administrative structure of public services, specifically of the public health system, in Sao Paulo. Our multi-level models assume that controlling for sub-prefecture membership completely accounts for the correlations that may exist between individuals living in the same sub-prefecture. The assumption is that, when subprefecture is accounted for, individuals are independent from each other.

This assumption may not hold true, however, as more than one person was allowed to participate per household. Having multiple individuals per household might have posed additional correlations across the participants of our study that remained unaddressed in our analysis. In order to best address this possibility, methods to account for correlation between individuals of the same household, such as having an additional random intercept for household in out analytical models, should have been conducted. Such analysis would have helped elucidate the degree to which the unaccounted correlation might have influenced our results.

Also, it is possible that there was correlation between the participants in each of the survey waves – some participated in several waves of the survey. This could have introduced bias in the sense that we may credit some changes (e.g., taking more or less drugs) to modifications in the behavior of the population over time (cohort effect), while they may be actually due to the aging of the sample (aging effect). In order to clarify the main underlying mechanism of this finding, a new wave of the survey with only new participants could be conducted, or, a longitudinal analysis of the existing sample, accounting for aspects of aging and survival, could be performed.

Fifth, the representativeness of our sample to the Sao Paulo older adult population relied on a major assumption: that the individuals who agreed to participate in the survey were not systematically different from those who did

not participate. This assumption may not necessarily hold. The wealthiest individuals in the country live in Sao Paulo, and arguably the poorest live there as well It is possible that participation in the survey might have been differential across the levels of income - wealthier and healthier individuals, especially those who were still working, might be harder to reach (the wealthy tend to live in gated communities in Sao Paulo), and might be less likely to agree to participate in the survey. Poorer and sicker individuals might be more restricted to the household, easier to locate, and more inclined to participate.

If true, this would have skewed the study sample towards sicker and poorer individuals. This possibility was not a matter of great concern to us, however. We did find significant differences in income across the participants. Some participants reported incomes that were thousands of times larger than others. Also, the main goal of our study was to inform policy-making aimed at mitigating polypharmacy. It is unlikely that public policies would significantly influence drug utilization among the extremely rich. These individuals are less likely to use services from the public health system, and are less likely to be sensitive to policies such as changes in formularies or other drug utilization incentives. Also, it can be argued that the constitutional mission of the public health system in Brazil prioritizes the health of the most vulnerable and underserved populations, and our results would be in line with that mission.

Lastly, the city of Sao Paulo has several particularities that must be pondered when considering the generalizability of our results to other areas in Brazil. Sao Paulo is by far the largest and most economically advanced city in the country. The social inequalities across its population and the heterogeneity across its geographic areas are striking. Its administrative division in sub-prefectures is unique. All these factors might compromise the generalizability of our results to other areas.

Yet, we argue that major urban centers in Brazil may still find value from our results. There are seventeen cities with over a million inhabitants in Brazil. Even if not at the same level of magnitude, these cities share with Sao Paulo the presence of stark social and economic inequalities and a decentralized model of decision-making in the public health system. Up to 85% of the population in Brazil is concentrated in major urban centers such as these large cities and their surrounding metropolitan areas. We believe that, at the very least, our results provide a basis for future investigations of polypharmacy in other Brazilian metropolitan areas. For example, we demonstrated that area-level factors are significantly associated with the likelihood of polypharmacy at the

individual level. Future studies of polypharmacy in other Brazilian cities should make sure to include community as well as individual characteristics in their models.

6.4 STRENGTHS

Our study benefitted from a very comprehensive survey that collected a wide range of demographic, socio-economic, health, behavioral, and health care utilization characteristics from the participants, including detailed information on the types of drugs in use. The survey was replicated three different times, using the same methodology and questionnaire, spanning a total period of 10 years. When weighted by the inverse probability of selection, the sample was representative of the non-institutionalized population of older adults living in Sao Paulo.

Other sources of data on drug utilization are largely unavailable in Brazil. Private insurance does not cover outpatient drugs in Brazil; hence, administrative claims data are not available. Drugs are purchased out-of-pocket, so pharmacy claims data are also not available. Many individuals obtain drugs from the public system. However, only drugs from a selected formulary are provided by the public health system. Any data from public drug provision would not capture the totality of drugs utilized by the population. Electronic health records are proprietary of certain health providers or insurers; they may not capture drugs that were self-prescribed or that were prescribed by out-of-network providers. Even if they were available, none of these sources would likely contain the same level of detailed patient-level information and be representative of the total population of older adults in Sao Paulo, which were two major strengths of our data.

The richness of the individual-level characteristics, combined with the geographic distribution of the participants – spanning all but one of the Sao Paulo sub-prefectures - allowed us to implement multi-level models to investigate the association of community-and health system-characteristics with polypharmacy while controlling for a large set of individual level factors. This structure was a major contribution of our study to the literature with polypharmacy.

Multi-level models are strongly recommended in social science research, especially to address issues of health care utilization, because these are multi-factorial and multi-level by nature (Phillips). In addition, multi-level models avoid the possibility of ecological fallacy.

Ecological fallacy occurs when associations estimated at the geographic level are interpreted as reflecting relationships at the individual level. By losing the information that links both exposures and outcomes at the individual level some associations may be true at the area level but not at the individual level. It is difficult to obtain data sources that allow for combining geographic and individual level data for the same unit of analysis, and multi-level investigations of the determinants of health care utilization are especially lacking in Latin America.

Our study provides a methodological structure that can be replicated in other Latin American cities. Similar surveys of older adults have been performed in major Latin American metropolitan areas (Palloni, 2002) and health systems in the region share some characteristics, contributing to the comparability of the findings.

We chose random effects models to control for the area level correlation. We could have used fixed effects models, but these might have allowed area membership (the effect of area) to be correlated to the other factors in the model.

Other strategies have been proposed in order to divide geographical areas for studies of regional variation in health care. In the United States, hospital referral regions, hospital service areas and metropolitan statistical areas have been utilized in such research and have been shown to yield similar results. In Sao Paulo it makes sense to use sub-prefectures as the unit of analysis, as they correspond to administrative divisions involved in health care provision. In addition, data on health services and population characteristics is reported at the sub-prefecture level by official public sources in Brazil.

6.5 FINAL CONSIDERATIONS

In some contexts the challenge is getting access to essential medicines. In others the problem is excessive or unsafe pharmaceutical use. Our study demonstrated that pharmaceutical use that is potentially excessive or unsafe is frequent among older adults in Sao Paulo. This should become a matter of public health concern.

We empirically demonstrated that polypharmacy is associated with greater levels of risk among this population. Drug-related risk can negatively affect health. When that occurs, drug risks can increase the burden of disease independently from the health conditions that motivated the drug use in the first place.

Public health actions to reduce the occurrence of polypharmacy in general, and riskier drug choices in particular, would help prevent drug-related morbidity and mortality. The benefits would not only improve the health of the Sao Paulo older adult population; they would also promote more efficient use of scarce public health resources.

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PERSONAL DATA

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EDUCATION AND TRAINING

2011-2016	Johns Hopkins Bloomberg School of Public Health	PhD
2009-2010	Princeton University	MPP
2006-2008	Universidade Federal do Rio Grande do Sul	MSc
2001-2004	Hospital de Clinicas de Porto Alegre	Neurology Residency
1995-2000	Universidade Federal do Rio Grande do Sul	MD

PROFESSIONAL EXPERIENCE

2007-present	UNIMED medical cooperative, Porto Alegre, Brazil	Attending Physician, Neurology
2012-present	Johns Hopkins Bloomberg School of Public Health	Research Assistant
2006-2017	Instituto de Previdencia do Rio Grande do Sul, Brazil	Attending Physician, Neurology
2007-2016	Hospital Moinhos de Vento, Porto Alegre, Brazil	Attending Physician, Neurology
2014-2014	JHPIEGO	Research Assistant
2011-2012	Johns Hopkins International Vaccine Access Center	Research Assistant
2011-2013	Brazilian Network for Health Technology Assessment	Consultant, High-Cost Medicines
2010-2011	Princeton University Center for Health and Wellbeing	Research Assistant
2009-2010	Hospital de Clinicas de Porto Alegre, Brazil	Researcher
2008-2009	Ministry of Health, Brazil	Consultant, High-Cost Medicines
2007-2009	General Attorney's Office, Rio Grande do Sul, Brazil	Medical Advisor, Pharmaceuticals
2005-2008	State Health Secretariat, Rio Grande do Sul, Brazil	Advisor, Pharmaceutical Policy
2005-2008	Hospital Luterano da ULBRA, Brazil	Instructor, Internal Medicine Residency
2004-2008	Hospital Luterano da ULBRA, Brazil	Attending Physician, Neurology

PROFESSIONAL ACTIVITIES

Society Membership and Leadership

2016-present	Health Systems Global
2007-present	UNIMED Medical Cooperative, Porto Alegre, Brazil
2013-2015	International Society of Pharmacoepidemiology (ISPE)
2007-2012	Health Technology Assessment International (HTAi)

Participation on Advisory Panels

2009-2010 Botulinum Toxin Clinical Protocols and Therapeutic Guidelines, Ministry of Health, Brazil

Program Development

2005-2008 Dystonia Reference Center, Health Secretariat of the Rio Grande do Sul state, Brazil

EDITORIAL ACTIVITIES

Peer Review Activities

2013-present International Journal for Equity in Health

2012-2015 Pan American Journal of Public Health

2012-2012 Heart Journal

HONORS AND AWARDS

Honors

2009 Distinguished Teaching, Universidade Luterana do Brasil

2008 Distinguished Teaching, Universidade Luterana do Brasil

2008 Baccalaureate Speaker, Class of Medical School Graduates, Universidade Luterana do Brasil

Awards

2016 David and Elinor Bodian Scholarship Award, JHSPH

2016 Henry K. and Lola Beye Scholarship in International Health, JHSPH

2015 Teaching-As-Research Fellowship, JHU Center for Educational Resources

2015 Gordis Teaching Fellowship, JHU Krieger School of Arts and Sciences

2013 Gordis Teaching Fellowship, JHU Krieger School of Arts and Sciences

2009-2009 Research Fellowship, Council for Scientific and Technological Development (CNPq), Brazil

2008-2009 Research Fellowship, Princeton University Grand Challenges Initiative and the Ford Foundation

1997-2009 Scientific Research Training Program, National Council for Scientific and Technological Development (CNPq), Brazil

PUBLICATIONS

Journal Articles (peer-reviewed)

- Lavoie M, Counts C, Fracica E, Socal MP, Anderson G. Options for Restoring Competition in the Generic Drug Industry. Article under review by *Medical Care Research and Review* journal.
- Socal MP. Patient Narratives: A Tool for Patient-Centered Health Systems Education. Article under review by *Health Education Research* journal.
- Socal MP, Trujillo AJ. Links Between Chronic Illness and Late-Life Cognition: Evidence From Four Latin American Countries. *J Aging Health*. 2016 Nov 10. pii: 0898264316674557.
- Biehl J, Socal MP, Amon JJ. The Judicialization of Health and the Quest for State Accountability: Evidence from 1,262 Lawsuits for Access to Medicines in Southern Brazil. *Health Hum Rights.* 2016 Jun;18(1):209-220.
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- Fernandes GC, Socal MP, Schuh AF, Rieder CR. Clinical and Epidemiological Factors Associated with Mortality in Parkinson's Disease in a Brazilian Cohort. *Parkinsons Dis.* 2015; 2015: 959304.

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- Biehl J, Amon JJ, Socal MP, Petryna A. Between the court and the clinic: lawsuits for medicines and the right to health in Brazil. *Health Hum Rights*. 2012 Jun 15;14(1):E36-52.
- Siebert M, Donis KC, Socal M, Rieder CR, Emmel VE, Vairo F, Michelin-Tirelli K, França M Jr, D'Abreu AC, Bettencourt C, Lima M, Lopes Cendes I, Saraiva-Pereira ML, Jardim LB. Glucocerebrosidase gene variants in parkinsonian patients with Machado Joseph/ spinocerebellar ataxia 3. *Parkinsonism Relat Disord*. 2012 Feb;18(2):185-90.
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- Rieder CR, Schestatsky P, Socal MP, Monte TL, Fricke D, Costa J, Picon PD. A Double-Blind, Randomized, Crossover Study of Prosigne Versus Botox in Patients With Blepharospasm and Hemifacial Spasm. *Clinical Neuropharmacology.* 2007 Jan-Feb;30(1):39-42.
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- Kowacs F, Socal MP, Ziomkowski SC, Borges-Neto VF, Toniolo DP, Francesconi CR, Chaves ML. Symptoms of Depression and Anxiety, and Screening for Mental Disorders in Migrainous Patients. *Cephalalgia*. 2003 Mar;23(2):79-89.
- Cunha GB, Rotta NT, Silva AR, Dieder AL, Wolf AL, Moser C, Silva FF, Socal MP, Silva PF, Margis R. Prevalence of prenatal exposure to cocaine in a sample of newborns from a university teaching hospital. *J Pediatr (Rio J*). 2001 Sep-Oct;77(5):369-73. [article in Portuguese].
- Kowacs F, Toniolo DP, Ziomkowski SC, Francesconi CRM,Chaves MLF. Migraine and Psychyatry Disorders. *Revista de Psiquiatria do Rio Grande do Sul*, 2001; 23(1): 19-36. [article in Portuguese].

Chapters

- Socal MP, Rieder CRM, Monte TL, Krug BC, Amaral KM. Distonias focais e Espasmo Hemifacial (Focal Dystonia and Hemifacial Spasm) In: Protocolos Clínicos e Diretrizes Terapêuticas (Clinical Protocols and Therapeutic Guidelines), 2nd Ed. Paulo Dornelles Picon & Alberto Beltrame, Eds. Brasília, DF, Brazil: Ministério da Saúde, 2010.
- Finkelsztejn A, Stefani MA, Cristovam RA, Moraes GS, Teixeira LB, Schneider SB, Socal MP, Finkelsztejn KRP, Nogueira L. Escalas em Neurologia (Scales in Neurology). In: Rotinas em Neurologia e Neurocirurgia (Routines in Neurology and Neurosurgery). Márcia Lorena Fagundes Chaves, Alessandro Finkelstejn & Marco Antônio Stefani, Eds. Porto Alegre, RS, Brazil: Artmed Editora, 2008.

Practice-Related Reports

- Constenla D, Mirelman A, Alvaro A, Chen A, Socal M. The economic value of vaccines and immunization programs in low- and middle-income countries: An annotated bibliography. International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. Baltimore, MD: August, 2012

- Gregory A, Kawamoto R, Lopez J, Palmer D, Petkun A, Socal M, Wong A, Woods G, Yin J. Implications for the Utilization of Advanced Medical Imaging: Comparative Effectiveness Research in the United States. Woodrow Wilson School, Princeton University: January 2010.

CURRICULUM VITAE

Mariana P. Socal, M.D., M.Sc., M.P.P., Ph.D.

PART II

TEACHING

Advisees

M.D. Thesis – Universidade Luterana do Brasil [in Portuguese]

2007

- Jean Franco Rostellato Marin, MD
  Neurological side effects of cefepime - drug-induced encephalopathy (cohort study)

2008

- Tiago Hermes Maeso Montes, MD
  Effects of methylphenidate on the memory of Wistar rats (experimental study)
- Fernando Godoy Neves, MD
  Comparison between different radiologic methods and macroscopic findings of ulcerations in carotid plaques (cross-sectional study)
- Marta Ryff Moreira, MD
  Comorbidity between attention deficit-hyperactivity disorder and bipolar disorder (review)
- Letícia Machado Rosa da Silva, MD
  Risk factors for late hospital arrival in patients with acute ischemic stroke (review)
- Ana Caroline Gazolla, MD
  Socio-demographic factors and time-to-arrival in patients with acute stroke (cross-sectional study)

2009

- Fernando Muratore, MD
  Cognitive scales used in the diagnosis of Alzheimer's disease in the Brazilian population (review)
- Eduardo Fialho Ruschel, MD
  Economic aspects of early- versus late-onset Parkinson's disease (review)
- Aline Tagliari Kurtz, MD
  Relationship between age of onset and predominant symptoms in Parkinson's disease (review)

General Internal Medicine Residency Capstone Project – Universidade Luterana do Brasil [in Portuguese]

2009

- Fabíola Madalozzo da Costa, MD
- Vanice Ferraza Zaltron, MD

Final Oral Exam Participation

M.D. Thesis Examination Committee – Universidade Luterana do Brasil [in Portuguese]

2007

- Thais Pletsch Schaefer. Relationship between brain information processing (as measured by evoked potentials) and training in computer games
- Bethânia Câmara Ehlers. Normal Values of Sensitive Nerve Conduction Studies in the Elderly.

2008

- Rodrigo Meirelles Borba. Differential diagnosis of Headache. A review

Classroom Instruction (Principal Instructor)
2015
Johns Hopkins University – Krieger School of Arts and Sciences
AS.280.409 Health Systems Challenges from Chronic Diseases in Low- and Middle-Income Countries
Students: 14

2013
Johns Hopkins University – Krieger School of Arts and Sciences
AS.280.409 Health Systems Challenges from Chronic Diseases in Low- and Middle-Income Countries
Students: 16

2006-2008
Universidade Luterana do Brasil – School of Medicine [in Portuguese]
Neuro-Psychiatry I
Students: 60

2006-2008
Universidade Luterana do Brasil – School of Medicine [in Portuguese]
Neuro-Psychiatry II
Students: 60

2005-2008
Universidade Luterana do Brasil – School of Speech Therapy [in Portuguese]
Introduction to Neurology
Students: 20

Other Significant Teaching
2016
Johns Hopkins Bloomberg School of Public Health
223.667.11 Chronic Diseases in Low and Middle Income Countries: Prevalence and Epidemiology
(The Summer Institute in Tropical Medicine and Public Health)
Lecturer in the module of brain disorders
Students: 10

2015
Johns Hopkins Bloomberg School of Public Health
223.667.11 Chronic Diseases in Low and Middle Income Countries: Prevalence and Epidemiology
(The Summer Institute in Tropical Medicine and Public Health)
Lecturer in the module of brain disorders
Students: 12

Teaching Assistantship
Johns Hopkins Bloomberg School of Public Health
2012-2013
140.621.01 Statistical Methods in Public Health I (4 credits)
140.622.01 Statistical Methods in Public Health II (4 credits)
221.647.01 Comparative Evaluation for Health Policy in International Health (3 credits)
221.652.01 Health Financing in Low and Middle Income Countries (3 credits)
313.632.01 Economic Evaluation III (3 credits)
221.617.01 Behavioral Economics in Health Decisions (2 credits)
2013-2014
551.607.01 Pharmaceuticals Management for Under-Served Populations (3 credits)
221.617.01 Behavioral Economics in Health Decisions (2 credits)
2014-2015
380.756.01 Poverty, Economic Development, and Health (4 credits)
309.670.01 Comparative Health Insurance (3 credits)
2015-2016

300.610.01 Public Health Policy (4 credits)
309.670.01 Comparative Health Insurance (3 credits)
313.793.11 Extended Exercises in Cost Effectiveness (2 credits)

RESEARCH GRANT PARTICIPATION

2011-2016

NIH Grant P30 AG024361
Princeton Center for the Demography of Aging
An exploratory study of the occurrence of pharmaceutical-induced aging symptoms in the United States and in Brazil
Principal Investigator: Joao Biehl, Princeton University
Level of funding: US$70,000
Responsibilities: Co-principal investigator

ACADEMIC SERVICE

Division and/or Department

2014-2015 International Health Departmental representative, JHSPH Student Assembly

School

2013-2016 Founder and President, Chronic Diseases & Aging Initiative, JHSPH Student Group
2016-2016 Student Representative, JHSPH Ethics Board
2014-2015 Member, Quality of Life Committee, JHSPH Student Assembly

University

2016-present Steering Committee, Princeton University Graduate Alumni Giving

2012-present Volunteer, Princeton University Graduate Alumni Giving
2015-2016 Mentor, JHU Public Health Connection Program
2007-2009 Admissions Committee, Internal Medicine Residency, Universidade Luterana do Brasil

PRESENTATIONS

International Scientific Meetings

2016

Socal MP, Anderson G. “Health Systems Determinants of Pharmaceutical Use among Brazilian Eldery”. 4th Global Symposium on Health Systems Research. (Vancouver, Canada) Nov 14-18 2016 (poster)

2015

Socal MP, Trujillo A. " Chronic Illness and Late-Life Cognitive Decline". Research on Aging Showcase. Johns Hopkins Center on Aging and Health. (Baltimore, USA) May 15 2015 (poster)

2013

Socal MP. “Access and Utilization of Medicines: The Role of Health Technology Assessment from a Health Systems Perspective” Pharmacogenomics: From Molecules to Medicine. (Engelberg, Switzerland) July 09-13 2013 (oral presentation)

2012

Socal MP, Uribe MV, Rao KD. “Serving all and serving well? The Brazilian universal healthcare system and the challenge of the equitable allocation of healthcare resources”. 2nd Global Symposium on Health Systems Research. (Beijing, China) 31 Oct- 3 Nov 2012 (oral presentation)

Socal, MP. “Measuring The Gap Between Demand And Access To Medicines In The Brazilian Public Healthcare System". 9th HTAi Health Technology Assessment International Annual Meeting 2012. HTA in Integrated Care for a Patient-Centered System. (Bilbao, Spain) (oral presentation)

Socal, MP. “Estimating Access To Health Services In Brazil Through A Market Frontier Analysis”. 9th HTAi Health Technology Assessment International Annual Meeting 2012. HTA in Integrated Care for a Patient-Centered System. (Bilbao, Spain) (poster)

2010

Picon PD, Gonzalez RS, Picon RV, Terra CD, Gertner A, Barbosa J, Socal M, Gonçalvez J, Petryna A, Biehl J. "Court decisions and pharmaceutical policy in Brazil: Odds for the patients and for the state". 7th HTAi - Health Technology Assessment International 2010 (Dublin, Ireland) (poster)

Picon PD, Gonzalez RS, Picon RV, Terra CD, Gertner A, Barbosa J, Socal M, Jardim PM, Petryna A, Biehl J. "The impact of plaintiff economic status on access to the legal system: Suing the state of medicines in Rio Grande do Sul, Brazil." 7th HTAi - Health Technology Assessment International 2010 (Dublin, Ireland) (poster)

2009

An analysis of claims of irreparable harm in lawsuits for access to medicines in the state of Rio Grande do Sul, Brazil. 6th HTAi—Health Technology Assessment International 2009 (Singapore, Singapore) (poster)

Demanding Treatment Access through Regular Administrative Pathways and through Lawsuits in Brazil. 6th HTAi—Health Technology Assessment International 2009 (Singapore, Singapore) (poster)

Claiming the Right to Medicines in Brazil through Public and Private Doctors and Lawyers: A Pilot Study. 6th HTAi—Health Technology Assessment International 2009 (Singapore, Singapore) (poster)

2008

Peer-review of Medical Prescription of Pramipexole in the Public Health System in the South of Brazil: Evidence of an Irrational Use of Dopaminergic Agonists for Parkinson´s Disease. 5th HTAi—Health Technology Assessment International 2008 (Montréal, Canada) (poster)

Progressive Multifocal Leuko-Enchephalopathy Induced by Monoclonal Antibodies—A Systematic Review of Literature: Preliminary Data. 5th HTAi—Health Technology Assessment International 2008 (Montréal, Canada) (poster)

2007

Implementation of Brazilian Guidelines for Botulinum Toxin: A Three-Year Follow-up of a Cost-reduction Strategy in the Public Health System of Rio Grande do Sul, Brazil. 4th HTAi - Health Technology Assessment International 2007 (Barcelona, Spain) (oral presentation)

2000

Cunha GB, Silva AR, Dieder AL, Wolf AL, Zambrano C, Silva FF, Pretto I, Oliveira J, Silva PF, Socal MP, Margis R, Weissheimer R, Rotta NT. Prevalence of Cocaine Prenatal Exposure Detected as Benzoilecgonine in Newborns VIII Congreso Anual de la Academia Iberoamericana de Neurología Pediátrica. (Spain) – abstract available in: Comunicaciones Revista de Neurologia, Espanha, v. 31, n. 3, p. 228-228, 2000.

Invited Lectures and Seminars

Johns Hopkins University

2017

Course: 309.670.01 Comparative Health Insurance. Main instructor: Gerard Anderson
Lectures: Revenue Collection
Universal Coverage in Low and Middle Income Countries

2016

Course: 309.670.01 Comparative Health Insurance. Main instructor: Gerard Anderson
Lecture: Universal Coverage in Low and Middle Income Countries

2015

Course: 309.670.01 Comparative Health Insurance. Main instructor: Gerard Anderson
Lecture: Universal Coverage in Low and Middle Income Countries

Course: 313.793.11 Extended Exercises in Cost Effectiveness (Summer Institute on Health Policy and Management). Main instructor: Greg De Lissovoy.
Lectures: Framing the study; patient population; comparators; outcomes; decision tree
Model parameters: clinical events. Data sources. Calculating event probabilities
Measures of "effect": natural units
Measures of effect: health state preference

2014

Course: Brasilia Without Borders Executive Program in Public Leadership. Main instructor: Carlos Castillo
Lecture: Between Policy and Justice: Access to Medicines in Brazil

Other [in Portuguese]
2015

Lecture: Socioeconomic Information in Parkinson's disease: How and why to Analyze.
Scientific Meeting of Movement Disorders Researchers. Hospital de Clínicas de Porto Alegre, Brazil.
2008

Lecture: Genetics of Parkinson's disease in the south of Brazil.
Scientific Meeting of the Department of Medical Genetics. Hospital de Clínicas de Porto Alegre, Brazil

Lecture: Neuropharmacology.
Graduate Studies program. Hospital Moinhos de Vento, Brazil.

Lecture: Evaluation of Syncope
Continued Medical Education Program, Universidade Luterana do Brasil
2007

Lecture: Frequency of genetic Parkinsonism in Rio Grande do Sul
Brazilian Congress of Brain, Behaviour and Emotions. Bento Gonçalves, RS, Brazil

Lecture: Pharmacoeconomic analysis of Multiple Sclerosis treatments
Brazilian Congress of Brain, Behaviour and Emotions. Bento Gonçalves, RS, Brazil

Lecture: Tremor and Parkinsonism.
Clinicasul, Regional Congress of Internal Medicine, Bento Gonçalves, RS, Brazil

Lecture: Medication-induced Movement Disorders
Scientific Meeting, Department of Neurology, Hospital de Clínicas de Porto Alegre, Brazil.

Lecture: Tremor – differential diagnosis and treatment
Scientific Week. Universidade de Passo Fundo, Brazil.
2006

Lecture: Headache
Continuing Medical Education Program, Universidade Luterana do Brasil

ADDITIONAL INFORMATION

Personal statement of research and practice goals, objectives and impact

Affordable, sustainable and qualified access to medicines is a challenge to countries worldwide, especially as their populations get older and chronic diseases become more prevalent. The appropriate use of medicines, an issue that cuts across all areas of medicine and medical care, is of great public health relevance globally. This is also an emerging issue in developing countries, which currently compose almost half of the world's pharmaceutical markets. I am committed to researching ways to safeguard sustainable, affordable, and appropriate access to pharmaceutical treatments for aging and chronically ill populations around the world.

Keywords

Pharmaceutical policy, access to medicines, drug pricing, drug safety, treatment appropriateness, health systems, health insurance, chronic diseases, low- and middle-income countries.